Kocatepe Tıp Dergisi
Kocatepe Medical Journal
2014;15(2):92-8

ÖZGÜN ARAŞTIRMA / RESEARCH STUDY

Induction or Adjuvant Docetaxel/ Cisplatin Chemotherapy in Advanced Stage Non-Metastatic Nasopharyngeal Cancer

Metastatik Olmayan İleri Evre Nazofaringeal Kanserde İndüksiyon veya Adjuvant Dosetaksel/Cisplatin Kemoterapisi

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Geliş Tarihi / Received: 22.11.2012 Kabul Tarihi / Accepted: 05.03.2013

ABSTRACT

Objective: Meta-analyses of randomized controlled trials was to determine the additional value of induction, concurrent, and/or adjuvant chemotherapy to radiation in the treatment of locally advanced nasopharyngeal carcinoma (NPC) with regard to the overall survival (OS)

Material and Methods: A total of 28 patients with loacally advanced NPC were included for this trial. Docetaxel (75 mg/m2 on Day 1) and cisplatin (75 mg/m2 on Day 1) were administered every 21 days, after or before which concurrent chemoradiotherapy (CCRT) was administered. The efficiency of the adjuvant or inductional docetaxel/cisplatin regime and the toxicity profile were retrospectively evaluated

Results: The objective response rate (ORR) was 75 % (13 partial responses, 8 complete responses). Stable disease (SD) was seen in 7 patients (25 %) whereas there was no progressive disease (PD). The median PFS for the induction chemoterapy group was 18.7 months and had not been reached for the adjuvant chemoterapy group. The 3-year PFS rates were 20 % and 66,9 %, respectively (p:0.79). The median OS for the induction chemoterapy group was 25.36 months and had not been reached for the adjuvant chemoterapy group. The 3-year OS rate was 26,7 % and 72,2 %, respectively (p:0.231).

Conclusion: In our study we demonstrated that the addition of adjuvant chemotherapy to CCRT did not additional benefit compared to hystorical data. Further studies are required to invastigate this hypothesis.

Keywords: Chemotherapy; adjuvant and induction chemotherapy; nasopharyngeal neoplasms.

ÖZET

Giriş: Randomize kontrollü çalışmaların meta-analizlerinde lokal ileri nazofaringeal karsinomada (NPC) indüksiyon, konkürrent ve/veya adjuvant kemoterapinin radyoterapiye ilave edilmesi overall survival (OS) ile ilişkili bulunmuştur.

Gereç ve Yöntem: Toplam 28 lokal ileri NPC li hasta çalışmaya dahil edildi. Dosetaksel (75 mg/m^2 / 1.gün) ve sisplatin (75 mg/m^2 / 1.gün) 21 günde bir konkürrent kemoradyoterapi öncesinde veya sonrasında verildi. Adjuvant veya indüksiyon dosetaksel/sisplatin rejiminin etkinliği ve toksite profili retrospektif olarak değerlendirildi

Bulgular: Objektif yanıt oranı (ORR) % 75 saptandı (13 parsiyel yanıt, 8 tam yanıt). Stabil hastalık (SD) 7 (% 25) hastada saptanırken progresif hastalık saptanmadı. İndüksiyon kemoterapi alan hastalarda progresyonsuz sağ kalım (PFS) 18.7 ay saptandı ve adjuvant kemoterapi alan grupta ise anlamlılığa ulaşmadı. 3 yıllık PFS oranları sırasıyla % 20 ve % 66,9 saptandı (p:0.79). Median OS indüksiyon kemoterapi grubunda 25.36 ay ve adjuvant alan grupta anlamlılığa ulaşmadı. Sırasıyla 3 yıllık OS aranları % 26,7 ve % 72,2 saptandı (p:0.231).

Sonuç: Bizim çalışmamızda konkürrent kemoradyoterapiye adjuvant kemoterapinin ilavesi geçmiş bilgilerle karşılaştırıldığında ilave fayda getirmediği gösterildi. Bu hipotezin araştırılması için daha ileri çalışmalar gereklidir.

Anahtar Kelimeler: Kemoterapi; adjuvant ve indüksiyon kemoterapisi; nazofaringeal tümörler.

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INTRODUCTION

NPC is different from other head and neck tumors regarding the means of etiology, geography and therapy. There are 80.000 new NPC cases reported every year and 50.000 deaths every year due to NPC (1). This tumor is rare in most geographical regions but is endemic in some regions of the world like southern China, Southeast Asia, and North Africa (2). In NPC, therapy varies according to the stages of the tumor. In advanced stages (stages III, IVa, and IVb), the recommended therapy is concurrent chemoradiotherapy (CCRT) (3- 5). Moreover, adjuvant chemotherapy is recommended as a supplement to CCRT, especially in high risk patients with a good performance. To the best of our knowledge there is no study available that compares CCRT alone with CCRT plus adjuvant chemotherapy, and for this reason, the efficiency of adjuvant chemotherapy is not entirely known. Until the data of phase III studies is revealed, therapy consisting of induction chemotherapy followed by CCRT therapy may be regarded as experimental. In cases in which the radiotherapy area is vast or the tumor can not be completely covered by radiotherapy (T4 tumor, N3 disease), induction therapy is recommended (6). However, this therapy may end up causing a delay in radiotherapy treatment. Regimes such as cisplatin/epirubicin,epirubicin/cisplatin/5-fluorouracil (5-FU) (ECF), paclitaxel/cisplatin/5-FU, cisplatin/5-FU (PF), cisplatin/docetaxel, and cisplatin/docetaxel/5-FU (DCF) have been studied as induction or adjuvant chemotherapy. The effect of taxanes in NPC has been previously shown (7).

In this study, 28 patients with a diagnosis of advanced stage NPC were given CCRT along with an adjuvant or inductional docetaxel/cisplatin regime, and the efficiency and the toxicity profile were retrospectively evaluated.

MATERIAL and METHODS

Patients

The data from 28 locally advanced non-metastatic NPC-diagnosed patients who were referred to the Medical Oncology Department of The Izmir Katip Celebi University Ataturk Training and Research Hospital between August of 2004 and April of 2011 was evaluated retrospectively. All of them had histologically proven, locally advanced disease. The Eastern Cooperative Oncology Group (ECOG) performance status was found to be between 0 and 2 in all cases. Pre-treatment evaluation included a complete medical history, physical examination, complete blood cell count, serum biochemistry, magnetic resonance imaging (MRI) of the head and neck, chest computed tomography (CT), and abdominal ultrasonography. All patients underwent physical examination along with complete blood count and serum biochemistry assessment every 21 days. Radiological assessment was repeated every three cycles.

Chemotherapy

Of the 28 patients who were retrospectively evaluated, five received induction and the remaining 23 received adjuvant chemotherapy. A docetaxel/ cisplatin regime was used as the induction or adjuvant chemotherapy. Administration of 75 mg/m² docetaxel in 500 ml 5 % dextrose solution and 75 mg/m² cisplatin in 500 ml 0,9 % NaCl solution was carried out as a 60 min iv infusion on day one. Cisplatin and the diuretic furosemide were given when the creatinine clearence was ≥ 60 ml/min and with pre- and post-hydration. If the creatinine clearance was < 60 ml/min, carboplatin AUC 6 in a 500 ml 5 % dextrose solution was administered as a 60 minute infusion instead of cisplatin. Premedication with fluocortolone (80 mg po) was given the day before treatment and continued on days one and two. Prophylactic antiemetic treatment was given routinely with a 5-HT blocker prior to chemotherapy administration. Primary prophylaxis was achieved by filgrastim or lenograstim in each cure of chemotherapy between days three and five. Patients receiving induction chemotherapy got two or three cures of chemotherapy depending on their chemotherapy response rates and their tolerance. Adjuvant chemotherapy was started three weeks after the completion of radiotherapy, and three or six cures were given depending on the patients' tolerance levels towards chemotherapy. Before each course was completed, blood cell counts and serum biochemistry were obtained. Treatment was given when neutrophiles were ≥ 1,500/µL, and platelets ≥ 100,000/µL. Dose reduction were planned for grade 3/4 National Cancer Institute Common Toxicity Criteria (NCI-CTC) grading system hematologic and non-hematologic toxicities other than alopecia and anemia. A maximum of two dose reduction levels were allowed (25 % or 50 %).

CCRT

Cisplatin 100 mg/m^2 per day or cisplatin 40 mg/m^2 per week was used as the chemotherapy regimen in CCRT. In patients with borderline renal functions, older age, or marginal performance status (ECOG 2 or worse), carboplatin or lesser doses of weekly cisplatin were administered. In patients with locally advanced stage disease, 6-MV x-rays were used as treatment in two regions parallel to the nasopharyngeal and neck lymph nodes and in one region anterior to the supraclavicular region. The conformal therapy technique was used in these patients. A dose of 50 Gy radiation was given to lower risk lymphatic regions and 60 Gy radiation was given to high risk areas. In addition, 66–70 Gy radiation was given to involved lymph nodes and 70 Gy to primary tumors. The procedure was completed over a period of seven weeks with a conventional fractionation of five days a week and 2 Gy fraction dose per day. In all patients, medulla spinalis was protected at 46 Gy level.

Radiotherapy and accompanying chemotherapy were postponed for a week in patients with neutrophiles < 1,500/µL or platelete levels of < 100,000/µL. In case of a grade 4 toxicity or deterioration of performance status, chemotherapy was stopped.

Response Evaluation

Tumor response to induction therapy was evaluated before commencement of CCRT by nasopharyngoscopy, physical examination, CT scan, and MRI. Tumor response after adjuvant chemoterapy was evaluated by nasopharyngoscopy and biopsy, physical examination, and CT scan six weeks after completion of CCRT. Tumor response was classified according to registered criteria.

Toxicity

Patients were evaluated for hematologic and non-hematologic toxicites. The NCI-CTC were used for this evaluation.

Stastistical analysis

The PFS and OS rates were calculated with the Kaplan-Meier method. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) for Windows version.15.0.

RESULTS

Patients

28 patients with NPC were evaluated retrospectively. The study group included nineteen (67,9 %) male andnine (32,1 %) female patients. The median age was 47 years old (range between;17- 74) . Allof the patients in the study group had ECOG performance status between 0-2.

The histopathologic examination showed one patient (3,6 %) with keratinized type I NPC, 25 patients (89,3 %) with nonkeratinized undifferentiated type II NPC, and two patients (7,1 %) with keratinized undifferentiated type III NPC. According to the T staging of the American Joint Committee on Cancer (AJCC), 13 patients (46,4 %) had T2 tumors, 9 patients (32,1 %) had T3 tumors, and 6 (21,4 %) had T4 tumors. According to the N staging of the AJCC, one patient (3,6 %) had N0 tumors, four of the patients (14,3 %) had N1 tumors, and 20 (71,4 %) had N2 tumors. The remaining three patients (10,7 %) had N3 tumors. Nineteen patients (67,9 %) had stage III tumors, and nine patients (32,1 %) had stage IV (21,4 % stage IVa, 10,7 % stage IVb) tumors when classified according to the stage grouping of the AJCC.

Five of the patients (17,8 %) received docetaxel/cisplatin regimen in a induction chemotherapy and the remaining 23 patients (82,2 %) received it in an adjuvant chemotherapy. The patients received median three cycles of chemotherapy. Dose reduction was required in eight of the patients (28,5 %) who received adjuvant chemotherapy. This reduction ratio was one patients who received induction chemotherapy. In both groups, the most common cause of dose reduction and delay in chemotherapy was upper and lower respiratory system infections. All patients received CCRT. The characteristics of the patients are summarized in Table I.

Efficacy

The response rates are summarized in Table II. Objective response rate (ORR) was 75 % [13 partial response (PR), 8 complete response (CR)]. Stable disease (SD) was observed in seven in patients (25 %) whereas were seen no progression in any of the patients .

At a median 22.9 months of follow-up, 10 patients (35,7 %) died and four patients (14,2 %)

developed distant metastasis. One had liver metastasis, two had distant lymph node metastasis, and the other patient had liver, lung, and lymph node metastases. The median PFS for the induction chemoterapy group was 18.7 months and had not been reached for the adjuvant chemoterapy group.

The 3-year PFSrates were 20 % and 66,9 %, respectively (p:0.79) (Figure I). The median OS for the induction chemoterapy group was 25.36 months and had not been reached for the adjuvant chemoterapy group. The 3-year OS rate was 26,7 % and 72,2 %, respectively (p:0.231) (Figure II).

The 3-year PFS rates according to gender were 87,5 % for female (95 % CI 46,5– 77,02 %), 41,3 % for males (95 % CI 24,3- 52,1 %),respectively (p:0.045). The 3-year OS rates were 87,5 % for female (95 % CI 56,7– 80,3 %), 50,8 % for men (95 % CI 25,1- 53,4 %), respectively (p:0.033).

Table I: Patient characteristics.

Patient characteristics		
No. of patients		28
Median age (year)		47 (17-74)
Male [No. (%)]		19 (67,9)
Female [No. (%)]		9 (32,1)
Median performance status (ECOG)*		1
Histologic type [No. (%)]		
	WHO type I	1 (3,6)
	WHO type II	25 (89,3)
	WHO type III	2 (7,1)
AJCC T stage		
	T1 [No. (%)]	0
	T2 [No. (%)]	13 (46,4)
	T3 [No. (%)]	9 (32,1)
	T4 [No. (%)]	6 (21,4)
AJCC N stage		
	N0[No. (%)]	1 (3,6)
	N1[No. (%)]	4 (14,3)
	N2[No. (%)]	20 (71,4)
	N3[No. (%)]	3 (10,7)
AJCC stage group**		
	Stage III [No. (%)]	19 (67,9)
	Stage IVa [No. (%)]	6 (21,4)
	Stage IVb [No. (%)]	3 (10,7)

*ECOG: Eastern Cooperative Oncology Group, ** AJCC :American Joint Committee on Cancer.

Table II: Clinical response results.

Clinical Response	**Number (%)**
CR	8 (28,6)
PR	13 (46,4)
SD	7 (25)
PD	0

CR: Complete remision, PR: Partial response, SD: Stable disease, PD: Progressive disease.

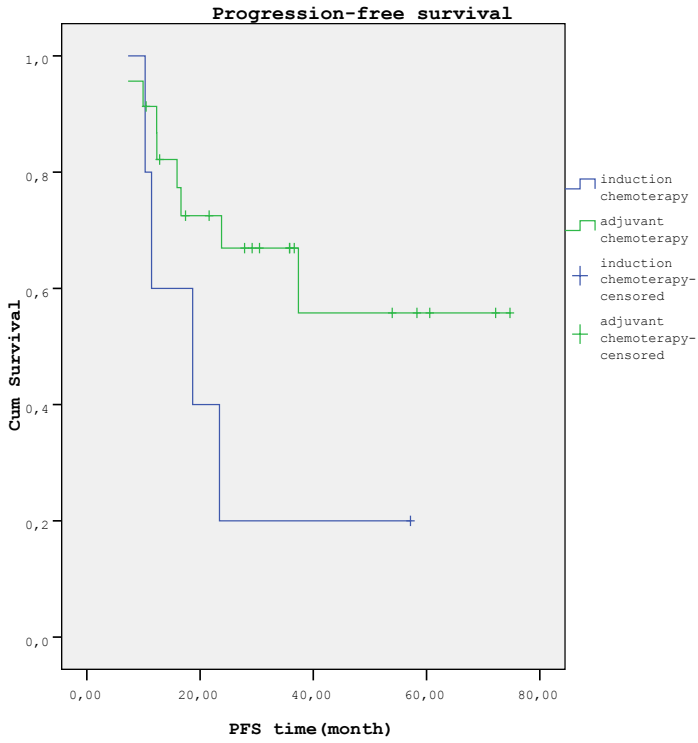

Figure I: Progression-freesurvival (PFS) Kaplan-Meier curve of the patients receiving induction and adjuvant chemotherapy.

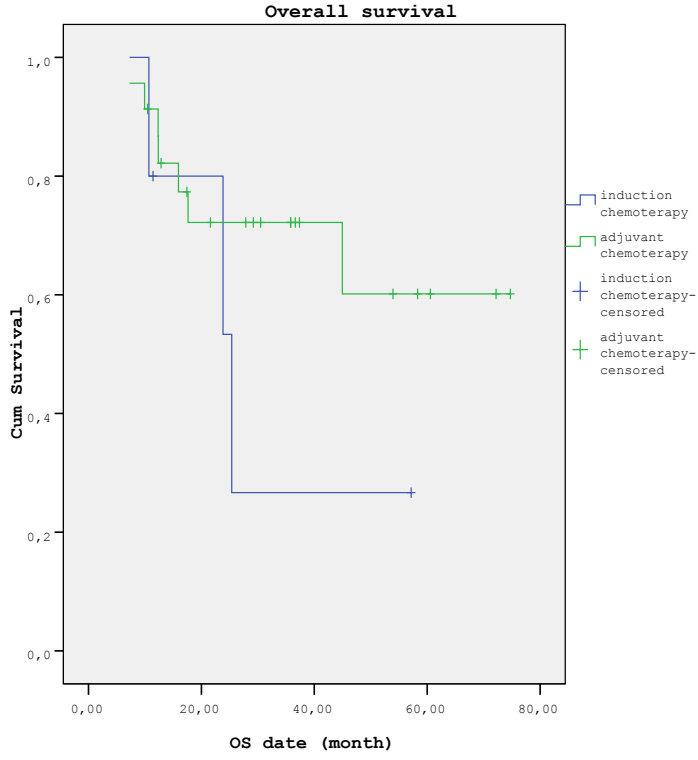

Figure II: Overall survival (OS) Kaplan-Meier curve of the patients receiving induction and adjuvant chemotherapy

Toxicity

The hematologic and non-hematologic toxicity rates are summarized in Table III. Grade 3 or 4 hematologic toxicity was observed in three patients (10,7 %). Febrile neutropenia was detected in one patient (3,6 %). Grade 3-4 nausea was seen in one patient (3,6 %), grade 3-4 stomatitis was present in two (7,1 %), and grade 3-4 diarrhea in one patient (3,6 %). Grade 1-2 neuropathy was also seen in one patient (3,6 %).

Table III: Treatment-related toxicity results.

Toxicity		Grade 1/2	Grade 3/4 no (%)
Hematologic			
	Neutropenia	4 (14,2)	2 (7,1)
	Anemia	2 (7,1)	-
	Trombocytopenia	1 (3,6)	1 (3,6)
	Febrile neutropenia	1 (3,6)	
Non-hematologic			
	Stomatitis	1 (3,6)	2 (7,1)
	Diarrhea	2 (7,1)	1 (3,6)
	Nause/vomiting	2 (7,1)	1 (3,6)

DISCUSSION

Concurrent chemoradiotherapy is recommed for advanced NPC disease (stage III, IVA, and IVB) by may outhers. Adjuvant chemotherapy has been a standard part of many concurrent chemoradiotherapy regimens, however its benefit is uncertain and toxicity is substantial Until more data in support of induction therapy are available, some experts suggest not using induction therapy for most patients with advanced nasopharyngeal carcinoma.

Al-Sarraf M et al was the first to demonstrate a benefit from CCRT for the treatment of locoregionally advanced nasopharyngeal cancer (3). In the same study, the 3-year PFS and OS rate for the CCRT groups were 69 % and 78 % , respectively. Chen Y et al evaluated the efficacy of concurrent chemoradiotherapy plus adjuvant chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma (8). The 2-year overall survival rate, failure-free survival rate for the concurrent chemoradiotherapy plus adjuvant chemotherapy and RT groups were 89,8 % vs. 79,7 % (p = 0.003), 84,6 % vs. 72,5 % (p = 0.001), respectively. This trial demonstrated the significant survival benefit of concurrent chemotherapy plus adjuvant chemotherapy in patients with locoregionally advanced NPC. Lee AW et al demonstrated that 5-year overall survival was similar in the concurrent-adjuvant chemotherapy to radiotherapy vs RT alone: 68 % vs 64 % (9).The results of a meta-analysis o indicate that concomitant chemotherapy in addition to radiation is probably the most effective way to improve OS in NPC (10). In a pooled data analysis of two phase III trials there was no improvement in prolonging survival (11). The trials investigating the efficacy of induction chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma followed by RT alone have failed to show an improvement in overall survival or pattern of relapse compared to RT alone (11, 12). In this study; The 3-year OS and PFS rates for induction vs adjuvant groups were 20 % and 66,9 % vs 26,7 % and 72,2 %, respectively. According to the inductionchemo-therapy, patients who received adjuvant chemotherapy had better OSand PFS rates. However the differance was naot statictically significant. The 3-year survival rates of the females and males showed were significantly different. Male patients were had worse prognoses than women (p:0.045 for PFS , P:0.033 for OS). The number of patients with stage 4 disease were higher than the number of female. This may explainthe survival difference according gender.

In conclusion, All of the studies demonstrated that addition of chemotherapy to radiotherapy improves survival. To date, there is stil no study that demonstrate the benefit of adding adjuvant chemotherapy to CCRT compared to CCRT alone. İn our study we demonstrated that the additionof adjuvantchemotherapytoCCRT did not additional benefit compared to hystorical data. Further studies are required to invastigate this hypothesis.

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