RESEARCH COMMUNICATION

Ifosfamide and Doxorubicin Combination Chemotherapy for Recurrent Nasopharyngeal Carcinoma Patients

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Abstract

Background: We assessed the efficacy and toxicity of ifosfamide and doxorubicin combination chemotherapy (CT) regimen retrospectively in Turkish patients with recurrent or metastatic nasopharyngeal carcinoma (NPC) previously treated with platinum-based chemotherapy. Methods: A total of thirty patients who had received cisplatin based chemotherapy/chemoradiotherapy as a primary treatment received ifosfamide 2500 mg/m^2 days 1-3, mesna 2500 mg/m^2 days 1-3, doxorubicin 60 mg/m2 day 1 (IMA), repeated every 21 days. Eligible patients had ECOG PS< 2, measurable recurrent or metastatic disease, with adequate renal, hepatic and hematologic functions. Results: Median age was 47 (min-max; 17-60). Twenty six (86.7 %) were male. Median cycles of chemotherapy for each patient were 2 (range:1-6). Twenty patients were evaluable for toxicity and response. No patient achieved complete response, with nine partial responses for a response rate of 30.0% in evaluable patients. Stable disease, and disease progression were observed in five (16.7%) and six (20.0%) patients, respectively. Clinical benefit was 46.7%. Median time to progression was 4.0 months. Six patients had neutropenic fever after IMA regimen and there were one treatment-related death due to tumor lysis syndrome in first cycle of the CT. No cardiotoxicity was observed after CT and treatments were generally well tolerated. Conclusion: Ifosfomide and doxorubicin combination is an effective regimen for patients with recurrent and metastatic NPC. For NPC patients demonstrating failure of cisplatin based regimens, this CT combination may be considered as salvage therapy.

Keywords: Nasopharyngeal carcinoma - ifosfamide - doxorubicin - chemotherapy - recurrent

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Introduction

As opposed to other head and neck cancers, NPC is highly prone to show locoregional and distant metastasis. It is well known that, metastasis develops within 3 years after the initiation therapy and following conventional definitive radiotherapy (RT), local recurrence or distant metastasis develops in about 20-30 % of patients. This ratio is reported as high as 38-87 % in autopsy series (Perez et al., 1992; Fong et al., 1996; Brady et al., 2010). In recurrent or metastatic disease where surgery and re-irradiation are not applicable, the main method of treatment is CT. To date, no randomized controlled trial, comparing different CT regimens in metastatic NPC is reported. However platinum containing combination regimens are accepted as first line due to high response rates. Different trials report response rates ranging from 29% to 56% with different chemotherapeutics in cases unresponsive to platinium based CT regimens. But there is no single regimen accepted generally as second line (Yeo et al., 1998; Chua et al., 2000; Huang et al., 2002; Foo et al., 2002; Ma et al., 2002; McCarthy et al., 2002; Chua et al., 2003; Chan et al., 2010). So it is important to define an effective second line regimen in the treatment of recurrent or metastatic NPC.

Ifosfomide; which is an analogue of cyclophosphamide; is a chemotherapeutic shown to be effective in testis cancer, lung cancer, sarcomas, pediatric tumors and nasopharyngeal cancer (Chua et al., 2000; Huang et al, 2002; Altundag et al., 2004). Anthracycline containing regimen has also been studied and proven to be effective in treatment of the NPC (Azli et al., 1995; Siu et al.,1998; Hasbini et al., 1999; Taamma et al., 1999; Huang et al., 2002; Onat H et al., 2002; Altundag et al., 2004). The aim of this study is investigating the efficacy of ifosfamide and doxorubicin combination as second line treatment in patients with recurrent and metastatic NPC.

Materials and Methods

From January 1999 to December 2010, the patients with recurrent and/or metastatic nasopharyngeal cancer

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previously treated with cisplatin containing regimen were analyzed retrospectively. A total of 30 patients were included in the study. The combination of ifosfamide 2500mg/m^2 days 1-3, mesna 2500mg/m^2 days 1-3, doxorubicin 60mg/m^2 day 1 (IMA), was repeated every 3 weeks. Depending on response, a total of two to six cycles were given. Patients who achieved at least disease stability after two cycles of this chemotherapy, were given additional two cycles. For responsive patients, a maximum of six cycles of treatment were given irrespective of the response rate. Treatment was stopped when response assessment after two cycles showed progressive disease, when there was evidence of progressive disease at any time or after six cycles of CT.

The statistical software SPSS for Windows (version 18) was used for statistical analysis.

Results

Thirty patients were included in the study. Patients' characteristics are shown in Table 1. Median age was 47 (min-max; 17-60). Twenty six (86.7%) patients were male. Twenty seven (90%) patients were classified as WHO Type 2 undifferentiated carcinoma, and 3 (10%) patients were classified as WHO Type 1 keratinizing squamous cell carcinoma. Median period of time from diagnosis to start of IMA regimen was 18 months (min-max; 5-108). Median time from last CT regimen to start of IMA regimen was 11 months (min-max; 1-89).

Before IMA, all patients had received cisplatin containing regimens. Twenty one (70 %) patients received CF (cisplatin and 5-Fluorouracil with a median number of 3 cycles) and 3 patients received DC (docetaxel and cisplatin with a median number of 3 cycles) as induction treatment. 2 patients received CF and 2 patients received DC in recurrence as palliative treatment. Two patients received only cisplatin with concomitant RT before starting salvage treatment with IMA.

Table 1. Patients and Disease Characteristics

Characteristics		Value
Gender (F/M)		4/26
Median age (year)		47 (17-60)
ECOG:	0	5 (16,7%)
	1	14 (46,7%)
	2	11 (36,7%)
Previous RT:	RT alone	21 (70.0%)
	Concurrent RT	8 (26,7%)
	No RT	1 (03,3%)
Previous CT regimens		
Cisplatin+5FU		23 (76,6%)
Docetaxel+cisplatin		5 (16,7%)
Cisplatin(with concomitant RT)		2 (06,6%)
Disease sites		
Locoregional disease		24 (80.0%)
No locoregional disease		6 (20.0%)
Distant metastasis		12 (40.0%)
No distant metastasis		18 (60.0%)
Distant metastasis sites:	Bone	5 (16,7%)
	Liver	1 (3.30%)
	Lung	6 (20.0%)
Median time from diagnosis to initiation of IMA chemotherapy		18 mo
Median time from last chemotherapy regimen to initiation of IMA chemotherapy		11 mo
Previous surgery		
Yes		6 (20%)
No		24 (80%)

Table 2. Treatment Outcome Based on Radiographic and Clinical Assessment

Response	Patients n (%)	Median time to progression (months)
Complete response	0	-
Partial response	9 (30.0%)	8 (1-18)
Stable disease	5 (16.7%)	3 (2-48)
Progressive disease	6 (20.0%)	2 (1-10)
Not assessable	10 (33.3%)	-

Table 3. Treatment Characteristics and Major Toxicities

Characteristics		Value
Median IMA cycles/patient		2
Neutropenic fever		6 (20.0%)
RBC transfusion		1 (3.30%)
G-CSF use		6 (20.0%)
Platelet transfusion need		3 (10.0%)
Gross hematuria		1 (3.30%)
Dose modification due to toxicity		7 (23.3%)
Tumor lysis and death		1 (3.30%)
İfosfamide encephalopathy		2 (6.60%)
Anemia:	Grade 1-2 anemia	17 (56.7%)
	Grade 3-4 anemia	2 (6.60%)
Neutropenia:	Grade 1-2 neutropenia	12 (40.0%)
	Grade 3-4 neutropenia	6 (20.0%)
Thrombocytopenia:	Grade 1-2	3 (10.0%)
	Grade 3-4	3 (10.0%)

At the beginning of the IMA regimen, 40% and 80% of the patients had distant metastasis and locoregional disease, respectively (Table 1). Median number of cycles of IMA regimen was 2, ranging between 1 and 6 cyles (Table-2).

Eleven patients received only one cycle of treatment; 6 patients were lost to follow up after first cycle; 2 patients developed ifosfamide encephalopathy on the third day of the first cycle. After switching ifosfamide to cyclophoshamide, one patient had a partial response at the end of sixth cycle and the other patient refused receiving further treatment. One patient who had liver and bone metastases developed tumor lysis syndrome on the second day of the treatment and died on seventh day of IMA regimen; one patient who had liver metastasis developed severe hepatotoxicity, hepatic coma and the treatment was stopped; one patient was admitted to intensive care unit because of severe pneumonia on the eight day of the IMA treatment and CT was stopped. One (3.3%) patient underwent radical neck dissection and 4 (13,3%) patients received palliative RT after CT.

None of the patients achieved complete response. Nine patients (30.0%) had a partial response, 5 (16,7%) patients had stable disease. Disease progression was observed in 6 (20.0 %) patients (Table 2). We were unable to evaluate response to treatment in 10 (33.3%) patients. The median time to progression for eligible 20 patients was 4 mo (min-max; 1- 48).

No significant difference in response rates was found between those who had previously received CF regimen as induction treatment or recurrent disease (p=0,973). There was one treatment related death due to tumor lysis. Two patients developed ifosfamide encephalopathy on the first cycle of IMA regimen. Six (20%) patients had a neutropenic fever episode after chemotherapy. One patient required RBC transfusion and 3 (10%) patients required platelet transfusion. G-CSF support was given to 6 (20%) patients. One patient experienced gross hematuria during IMA CT that resolved after increasing the dose of mesna. Dose modification became necessary in 7 (23,3%) patients because of the toxicities mentioned above. No acute and chronic cardiotoxicity was seen during or after IMA regimen (Table 3).

Discussion

Despite the similar ratios reported in studies about incidences of NPC, course of the disease was changed through new treatment modalities (Wei et al., 2010; Wei et al., 2010). Due to the tecniquel development of RT and incorporation of chemoradiation, high local control rates was achieved in the treatment and distant metastasis became more common presentation of recurrence in NPC (Razak et al., 2010).

To date, there is no randomized trial comparing the efficacy of any type of CT with supportive treatment in the management of metastatic NPC (Ma et al., 2008). Early trials investigating the most efficacious therapy in metastatic disease are all phase II, nonrandomized trials in which a platin based regimen is usually used. It is difficult to compare these studies since they show extreme heterogeneity in aspects such as number of patients, involvement criteria, stage of disease and previous CT and RT regimens. Despite the 5-30% of complete response rates reported in these phase II trials, it is well known that the disease recurs in 5-10 months and survival is not more than 12-18 months in metastatic NPC (Boussen et al., 1991; Auet al., 1994; Siu et al.,1998; Yeo et al.,1998; Taamma et al., 1999; Ngan et al., 2002; ; Chua et al., 2005; Leong et al., 2005; Chan et al., 2007). Studies in which newer chemotherapeutic agents combined with cisplatin, report a 25-75% of total response rate and a median survival of 9, 5 to 15 months (Ma et al., 2002; McCarthy et al., 2002; Ngan et al., 2002; Chua et al., 2003; Chua et al., 2005; Wang et al., 2008).

There is no standard regimen suggested for cases who received a platin based regimen beforehand and who have resistant disease. Ifosfamide and doxorubicin are agents which have been studied in such patients who received a platin based regimen beforehand and who have resistant disease (Chua et al., 2000; Huang et al., 2002). It is not possible to make a head to head comparison of our study with other studies on this subject, since the involvement criteria are variable and we have a small study population. However, when compared to studies with platin based regimens mentioned above, our study showed a lower total response rate (46,7%) and a shorter (4 months) median time to progression. Six patients developed neutropenic fever during treatment, G-CSF is given to all and none of them progressed to sepsis. We think that this result is related to strict application of evidence based therapy guidelines and proper dose modification of the drugs.

To date, there is no study to report any survival benefit or contribution to quality of life with any CT regimen in metastatic NPC. Randomized studies comparing standard platin containing regimens with the regimens like IMA which is given mainly for palliation will be useful. Additionally, quality of life and palliation of symptoms in metastatic NPC are the other important subjects waiting for proper assessment in randomized studies.

In summary, ifosfamide doxorubicin combination is an alternative for salvage therapy in patients with resistant NPC, if the toxicities are well controlled. However one should bear in mind that response duration provided by this regimen is not long and that it has a limited effect on survival.

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References

Altundag K, Aksoy S, Gullu I, et al (2004). Salvage ifosfamide-doxorubicin chemotherapy in patients with recurrent nasopharyngeal carcinoma pretreated with Cisplatin-based chemotherapy. *Med Oncol*, **21**, 211-5.

Au E, Ang PT (1994). A phase II trial of 5-fluorouracil and cisplatinum in recurrent or metastatic nasopharyngeal carcinoma. *Ann Oncol*, **5**, 87-9.

Azli N, Fandi A, Bachouchi M, et al (1995). Final report of a phase II study of chemotherapy with bleomycin, epirubicin, and cisplatin for locally advanced and metastatic/recurrent undifferentiated carcinoma of the nasopharyngeal type. *Cancer J Sci Am*, **1**, 222-9.

Boussen H, Cvitkovic E, Wendling JL, et al (1991). Chemotherapy of metastatic and/or recurrent undifferentiated nasopharyngeal carcinoma with cisplatin, bleomycin, and fluorouracil. *J Clin Oncol*, **9**, 1675-81.

Chan AT, Grégoire V, Lefebvre JL, et al (2010). Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, **21**, 187-9.

Chan ATC, Ma B, Tung S, et al (2007). Biweekly gemcitabine and oxaliplatin (GEMOX) in first-line metastatic or recurrent nasopharyngeal carcinoma (NPC) an early report. *J Clin Oncol Proc Am Soc Clin Oncol*, **25**, 6071.

Chua DT, Kwong DLW, Sham JS, et al (2000). A phase II study of ifosfamide, 5-fluorouracil and leucovorin in patients with recurrent nasopharyngeal carcinoma previously treated with platinum chemotherapy. *Eur J Cancer*, **36**, 736-41.

Chua DT, Sham JS, Au GK, et al (2003). A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. *Oral Oncol*, **39**, 361-6.

Chua DT, Sham JS, Au GK, et al (2005). A phase II study of docetaxel and cisplatin as first-line chemotherapy in patients with metastatic nasopharyngeal carcinoma. *Oral Oncol*, **41**, 589-95.

Fong KW, Chua EJ, Chua ET, et al (1996). Patient profile and survival in 270 computer tomography-staged patients with nasopharyngeal cancer treated at the Singapore general

hospital. *Ann Acad Med Singapore*, **25**, 341-6.
Foo KF, Tan EH, Leong SS, et al (2002). Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. *Ann Oncol*, **13**, 150-6.
Guo Y, Glisson BS (2010). Systemic treatment for incurable recurrent and/or metastatic nasopharyngeal carcinoma. In 'Nasopharyngeal cancer multidisciplinary management. Eds Lu JJ, Cooper JS and Lee AWM. Springer –Verlag Berlin Heidelberg, pp 267-75.
Hasbini A, Mahjoubi R, Fandi A, et al (1999). Phase II trial combining mitomycin with 5-fluorouracil, epirubicin, and cisplatin in recurrent and metastatic undifferentiated carcinoma of nasopharyngeal type. *Ann Oncol*, **10**, 421-5.
Huang HQ, Zhou ZM, Li YH, et al (2002). Preliminary results of ifosfamide and doxorubicin regimen in treatment of patients with recurrent and metastatic nasopharyngeal carcinoma. *Ai Zheng*, **21**, 409-11.
Leong SS, Wee J, Tay MH (2005). Paclitaxel, carboplatin, and gemcitabine in metastatic nasopharyngeal carcinoma: a phase II trial using a triplet combination. *Cancer*, **103**, 569-75.
Ma BB, Hui EP, Chan AT, et al (2008). Systemic approach to improving treatment outcome in nasopharyngeal carcinoma: current and future directions. *Cancer Sci*, **99**, 1311-8.
Ma BB, Tannock IF, Pond GR et al (2002). Chemotherapy with gemcitabine-containing regimens for locally recurrent or metastatic nasopharyngeal carcinoma. *Cancer*, **95**, 2516-23.
McCarthy JS, Tannock IF, Degendorfer P, et al (2002). A phase II trial of docetaxel and cisplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. *Oral Oncol*, **38**, 686-90.
Ngan RK, Yiu HH, Lau WH, et al (2002). Combination gemcitabine and cisplatin chemotherapy for metastatic or recurrent nasopharyngeal carcinoma: report of a phase II study. *Ann Oncol*, **13**, 1252-8.
Onat H, Basaran M, Esassolak, et al (2002). High-dose epirubicin and cisplatin in locally advanced undifferentiated nasopharyngeal carcinoma. *Clin Oncol*, **14**, 449-54.
Perez CA, Devineni VR, Marcial-Vega V, et al(1992). Carcinoma of the nasopharynx: factors affecting prognosis. *Int J Radiat Oncol Biol Phys*, **23**, 271-80.
Razak AR, Siu LL, Liu FF et al (2010). Nasopharyngeal carcinoma: the next challenges. Eur J Cancer, 46, 1967-78.
Siu LL, Czaykowski PM, Tannock IF, et al (1998). Phase I/II study of the CAPABLE regimen for patients with poorly differentiated carcinoma of the nasopharynx. *J Clin Oncol*, **16**, 2514-21.
Taamma A, Fandi A, Azli N, et al (1999). Phase II trial of chemotherapy with 5-fluorouracil, bleomycin, epirubicin, and cisplatin for patients with locally advanced, metastatic, or recurrent undifferentiated carcinoma of the nasopharyngeal type. *Cancer*, **86**, 1101-8.
Wang J, Li J, Hong X, et al (2008). Retrospective case series of gemcitabine plus cisplatin in the treatment of recurrent and metastatic nasopharyngeal carcinoma. *Oral Oncol*, **44**, 464-70.
Wei KR, Yu YL, Yang YY, et al (2010). Epidemiological trendsof nasopharyngeal carcinoma in China. *Asian Pac J Cancer Prev*, **11**, 29-32.
Wei K, Xu Y, Liu J, et al (2010). No incidence trends and no change inpathological proportions of nasopharyngeal carcinoma in Zhongshan in 1970-2007. *Asian Pac J Cancer Prev*, **11**,1595-9.
Yeo W, Leung TW, Chan AT, et al (1998). A phase II study combination of paclitaxel and carboplatin in advanced nasopharyngeal carcinoma. *Eur J Cancer*, **34**, 2027-31.