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ORIGINAL ARTICLE

The efficacy and safety of induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF) in treating patients with locally advanced nasopharyngeal carcinoma

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Induction chemotherapy;
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Abstract *Introduction:* This phase II clinical trial aimed to investigate the efficacy and safety of induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF regimen) followed by concurrent chemoradiation in patients with locally advanced nasopharyngeal carcinoma.

Methods: Eligible patients were aged 15–70 years and had to have newly diagnosed locally advanced NPC (T3–T4 and/or N2–N3, M0), Karnofsky Performance Status (KPS) $\geqslant 70$, and normal or adequate kidney, liver, cardiovascular, and bone marrow functions. All patients were assigned to receive 3 cycles of induction chemotherapy in an outpatient setting every 3 weeks with TPF regimen (docetaxel 75 mg/m^2 for day 1, cisplatin 75 mg/m^2 for day 1, 5-FU 750 mg/m^2/day with 8-h infusion on days 1–3) followed by 7 weeks of concurrent chemoradiation (70 Gy) with weekly cisplatin 30 mg/m^2.

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Results: Overall, 74 courses of induction chemotherapy were administered. After induction chemotherapy, overall response rate was 84%. However, only one patient achieved a pathologic complete response. At the end of concurrent chemoradiation, 24 patients (96%) achieved clinical and pathologic complete response at both nasopharynx and regional nodes and one (4%) had persistent disease. Treatment-related toxicities were common but manageable. Grade 1–2 anemia was the most hematologic toxicity being detected in 51 cycles (68.9%) of induction chemotherapy. Four patients developed uncomplicated, culture-negative febrile neutropenia. There was no treatment-related death.

Conclusion: Induction chemotherapy with TPF regimen followed by concurrent chemoradiation is highly effective with manageable toxicity in patients with locally advanced nasopharyngeal carcinoma.

1. Introduction

Despite the low incidence rate of nasopharyngeal carcinoma (NPC), the age distribution for NPC is younger than that for other head and neck sites. Approximately 20% of the patients are younger than 30 years of age.[1] It is also the most frequent carcinoma of the head and neck malignancy in pediatric and young adolescent population.[2] Locally advanced NPC refers to a group of NPCs demonstrating advanced disease in nasopharynx or regional lymph nodes without evidence of distant metastasis. Approximately 50% of NPCs are locally advanced at presentation.[3] Compared to other head and neck cancers, surgery plays a limited role in treating NPC. Distinctive anatomical location and vicinity of NPC to skull base neurovascular structures prevent curative surgery.[4,5] However, NPC is a highly radiosensitive tumor and radical external beam radiotherapy with or without chemotherapy remains the mainstay of treatment for this neoplasm. Concurrent chemoradiation is currently the standard of care for locoregionally advanced NPCs.[5] Locoregional and systemic failures are high in patients with locally advanced disease and contribute to poor survival.[4–6] Consequently, more effective chemotherapeutic regimens and other systemic therapy are needed to decrease the rate of locoregional and distant failure and improve survival.

Previous studies confirmed the efficacy and the feasibility of induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF regimen) regimen in locally advanced head and neck cancers.[7,8] In addition, the tolerability and efficacy of concurrent chemoradiation with weekly cisplatin have been proven in patients with locally advanced NPC. The present phase II clinical trial aimed to investigate the response rates of induction chemotherapy with TPF regimen followed by concurrent chemoradiation in treatment of locally advanced NPCs.

2. Patients and methods

This phase II clinical trial enrolled 28 patients with diagnosis of NPC who were referred to Namazi academic hospital for treatment between April 2011 and March 2012. Eligible patients were aged between 15 and 70 years and had to have newly diagnosed locally advanced NPC stage classification III–IV_B (T3–T4 and/or N2–N3, M0) based on the criteria used in the 7th edition of the American Joint Committee on Cancer (AJCC) Staging system,[9] Karnofsky Performance Status (KPS) $\geqslant 70$, and normal or adequate kidney, liver, cardiovascular, and bone marrow functions. In this study we considered a serum creatinine < 1.4 mg/dl, and creatinine clearance > 60 ml/min as adequate renal function. The study was approved by the Clinical Research Ethics Committee of Shiraz University of Medical Sciences in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Written informed consent was obtained from all patients before trial entry. Exclusion criteria were prior therapy, any evidence of distant metastases before or during the trial, known contraindication for chemotherapy (such as allergy to taxan drugs), positive history of receiving radiotherapy for other head and neck neoplasms, documented heart, liver, renal or blood coagulation diseases, and patients' refusal to participate in the trial or to sign on the consent form.

2.1. Patient evaluation

Pre-treatment evaluation included a complete medical history, physical examination with special attention on the status of cervical lymph nodes regarding their size, location and fixation, assessment of KPS, direct nasopharyngoscopy to determine tumor extension and taking biopsy, chest radiograph, ultrasound imaging of the abdomen and contrast-enhanced Computed Tomography (CT) scan of the nasopharynx and neck. Disease staging was defined according to the 7th edition of AJCC staging system.[9] Other tests included complete blood count (CBC), liver function tests (LFT) and renal function test (RFT). Baseline audiogram was performed for all patients. Whole body bone scintigraphy was performed in symptomatic patients or those with elevated alkaline phosphatase level. In addition, cardiovascular evaluation was carried out in high risk patients (age greater than 60 years, heavy smoker and background diseases like hypertension or diabetes mellitus). All patients were carefully evaluated for dental carry and all needed dental repairs and treatment were completed well before starting radiation therapy.

2.2. Treatment

All patients were assigned to receive induction chemotherapy in an outpatient setting every 3 weeks for 3 cycles with TPF regimen (docetaxel 75 mg/m^2 for day 1, cisplatin 75 mg/m^2 for day 1, 5-FU 750 mg/m^2/day with 8-h infusion on days 1–3). Antiemetic medication including a selective 5-hydroxytryptamine-3 (5HT3) antagonist and steroids were prescribed intravenously for all chemotherapy cycles. In addition, prophylactic colony stimulating factor (as 5 μg/kg filgrastim) was considered for all patients following each cycle of TPF regimen during days 5–9. Clinical condition, regional lymph