Induction Chemotherapy with Paclitaxel and Cisplatin, Followed by Concomitant Cisplatin and Radiotherapy for the Treatment of Locally Advanced Nasopharyngeal Carcinoma

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ABSTRACT

Purpose: To evaluate the efficacy and outcome of neoadjuvant paclitaxel and cisplatin chemotherapy followed by concurrent cisplatin and irradiation in patients with locally advanced nasopharyngeal (NP) squamous cell carcinoma.

Patients and Methods: The trial included 36 patients with locally advanced nasopharyngeal squamous carcinoma presented to Radiation Oncology and Otolaryngology departments - Ain Shams university hospitals, and Sohag Cancer Center between November 2002 and March 2006. Eligible patients were treated first with three cycles of induction chemotherapy (IC), paclitaxel (175mg/m² on day 1) and cisplatin (80mg/m² on day 1) followed by concomitant conventionally fractionated radiation (70Gy in 2Gy fractions) and cisplatin 20-mg/m²/day on days 1-5, 22-26 and 43-47 of the radiation therapy.

Results: Twenty nine patients (80%) and 32 patients (89%) achieved objective response after IC and concomitant chemoradiation (CCRT) respectively. The actuarial 3 years survival was 68%, and the actuarial 3 year progression free survival (PFS) was 66%. Survival and PFS were significantly better for patients with smaller tumor volume (stage III), compared with patients with stage IV. Thirteen patients (36%) have elements of local and/or regional failure and 5 patients (14%) have an element of distant metastasis. Neutropenia (25%), mucositis (22%) and vomiting (20%) were the most severe toxicities recorded (grade 3 and 4) during IC while mucositis (36%), dermatitis (28%), anemia (14%) and vomiting (14%) were the most pronouncing toxicities (grade 3 and 4) during CCRT.

Conclusions: IC followed by CCRT treatment program is feasible, tolerable and safe. This strategy improved local control and distant disease control. However combined treatment program have failed to improve survival rates over the historical result of CCRT trials.

Key Words: Nasopharynx – Radiation – Paclitaxel – Cisplatin.

INTRODUCTION

For many decades, radiotherapy was the standard treatment for locally advanced nasopharyngeal carcinoma (NPC) with local recurrence, distant metastasis and 5-year survival rates of 15%-50%, 20%-40% and 24%-52% respectively [1-3]. The Intergroup 0099 study (IGS) was the first to show a survival benefit with chemoradiation in locally advanced NPC which compared radiation therapy alone with cisplatin based concurrent chemoradiation (CCRT) and adjuvant chemotherapy [1]. Overwhelming evidences from randomized studies and recent systematic meta-analysis now support the use of concurrent cisplatin based CCRT as the standard of care for treatment of locally advanced NPC [4-8]. However, the prognosis still remains poor with CCRT because it is technically difficult to irradiate the whole tumor target to cancericidal dose without exceeding the tolerance of critical structures especially for tumors with parapharyngeal or intracranial extensions (T4) or those with high N stage (N2-3). In addition, despite the use of chemoradiotherapy, distant metastases remain the predominant site of treatment failure. Distant metastasis rate was as high as 36% [9-11]. Studies trying to improve the results through the addition of adjuvant or neoadjuvant chemotherapy to chemoradiotherapy are ongoing.
Patient tolerance to adjuvant chemotherapy is limited by the cumulative toxic effects of concurrent chemoradiotherapy [1,12-16]. The poor compliance with adjuvant chemotherapy after concurrent chemoradiation can be overcome by the use of neoadjuvant chemotherapy.

Building upon these informations, we conducted this phase II study in which induction chemotherapy (IC), paclitaxel and cisplatin followed by concomitant chemoradiation (CCRT) was used in an effort to eradicate micrometastases, while still providing adequate local control. Paclitaxel was selected for induction therapy with cisplatin as it was proved to be an active drug in NPC [17]. The primary end point of the study was locoregional control, survival, and progression free survival (PFS), and distant metastasis. The second end point of the study was toxicity.

PATIENTS AND METHODS

This trial included 36 patients with locally advanced nasopharyngeal squamous carcinoma presented to Radiation Oncology and Otolaryngology departments - Ain Shams university hospitals, and Sohag Cancer Center between November 2002 and March 2006.

Pretreatment evaluation:

Initial evaluation included: History, and physical examination, complete blood count, serum chemistries, chest X-ray and baseline audiometry. Local and regional tumor extents were assessed by computerized tomographic scan (CT scan), and/or magnetic resonance imaging (MRI), and fiberoptic examination of the upper aero-digestive tract including the nasopharynx, oropharynx, hypopharynx and larynx.

Eligibility:

Eligible patients were above 18 years old but not more than 70 years old with biopsy proven WHO NPC, of stage III or IV disease according to AJCC/UICC 1997 staging system [18]. Other eligibility criteria were ECOG performance status (PS) of ≤2, absolute neutrophil count (ANC) ≥1500/uL, platelets ≥100,000/uL, hemoglobin ≥10gm% creatinine clearance (CrCl) ≥60mL/min, bilirubin <2mg/dL, and transaminases levels < three times the upper normal limit, no evidence of distant metastasis, prior malignancy, prior chemotherapy or radiotherapy to the head and neck region. Dental extraction deemed necessary were performed before radiation therapy. Each patient gave written informed consent before entering the study.

Treatment plan:

Induction chemotherapy: Consisted of 2 cycles of paclitaxel (175mg/m² on day 1) followed by cisplatin (80mg/m² on day 1), one cycle every 3 weeks. Those who achieved at least clinical and radiological partial response to chemotherapy received an additional cycle of chemotherapy. Thirty minutes prior to paclitaxel administration, all patients should receive the following intravenous premedications: 20mg dexamethazone, 50mg diphenhydramine and 300mg cimetidine. Cisplatin was given intravenously, with standard pre and post-treatment hydration. Cisplatin was given during a 2-hour period of forced hydration. Dexamethazone was also administered intravenously or orally at a dose of 4mg/6 hours until the following morning. Antiemetic included ondansetron or granisetron IV during a period of 30 minutes before starting chemotherapy was effective in controlling emesis.

Dose modification for Toxicity:

A new cycle of chemotherapy was postponed until recovery if ANC was <1500/uL and platelet count was <100,000/uL, then a 25% dose reduction in subsequent cycles of paclitaxel and cisplatin in case of grade 3-4 neutropenia and/or thrombocytopenia developed. For patients with Cr Cl between 40 to 60mL/min, carboplatin targeting an area under the curve of 5 (Calvert formula) was to be substituted for cisplatin. If the nadir of the Cr Cl was <40mL/min or the patient developed otologic grade 3 or worse toxicity, cisplatin was stopped totally. IC was discontinued permanently in case of grade ≥2 neurologic toxicity. In case of symptomatic arrhythmia or AV block, paclitaxel infusion was stopped.

Concomitant chemoradiotherapy:

Radiation treatment was planned to begin 3 weeks after the last cycle of chemotherapy. Radiation therapy was administered with Cobalt-60 machine or 6-MV linear accelerator. The patients were treated in supine position with hyperextended neck. The patient’s head was fixed using special fixing device or face mask.
The patients were treated through 2 parallel opposing field and lower neck field. Two lateral opposed fields were used to treat the nasopharynx and adjacent structures and the upper neck lymph nodes. The upper border of the fields split the pituitary fossa. In case of base of skull involvement, the upper border was at least 1 cm higher. The anterior border encompassed the posterior 2 cm of the nasal cavity and maxillary antrum; in case of anterior extension, the border was moved forward 2 cm to cover the ethmoid and maxillary sinus with adequate margin. The posterior border was set behind the spinous process of C2 vertebra. The lower border of the field was placed at the level of thyroid notch or as low as the shoulder can permit. Dose was specified at the central axis on the midplane. The lower cervical lymph nodes and the supraclavicular lymph nodes were treated through an anterior lower neck field at 3 cm depth. The inferior border of the anterior field was 1 cm below the clavicles with shielding of lung apex. The lower anterior neck field matched the lateral fields on the skin by separating the two fields by 1/2 cm to avoid the overlap on the spinal cord at the junction of the fields. The lateral border was placed at the junction of medial two thirds and the lateral third of clavicle.

The basic treatment was given as 2 Gy / fraction, once a day; 5 days/week to a total dose of 50 Gy in 25 fractions. At 46 Gy, the lateral fields were reduced to spare the spinal cord. The posterior neck was supplemented with either posterior electron beam (9-12 MeV) field, or in case of Cobalt-60 machine, with oblique off cord boost fields. Clinically and radiologically negative neck and supravacular lymph nodes received a total dose of 50 Gy. An additional 20 Gy / 2 Gy / fraction were given to reduced volumes encompassing the nasopharynx, tumor extensions and clinically/radiologically positive nodes based on the pretreatment CT scan using shrinkage field technique. To supplement the dose to the clinically positive posterior neck nodes, boost techniques using electron beam (9-12 MeV) were used. Residual resectable cervical lymph nodes can be removed through neck dissection, 4 weeks after radiation.

During radiation, cisplatin was given intravenously in a dose of 20 mg/m^2/day from days 1-5, days 22-26 and days 43-47 of the radiation therapy days. The chemotherapy was given at approximately 60 minutes before receiving radiotherapy. If carboplatin needed to be substituted for cisplatin, during radiation, the dose was to target an area under the curve of 4 according to the Calvert formula, divided into five equal doses.

**Follow-up:**

The patients were evaluated by complete physical examination before each cycle of IC. Any clinical evidence of disease progression during IC should be confirmed by CT scan and fiberoptic nasopharyngoscopy. CT scan and fiberoptic nasopharyngoscopy were done two weeks after the second cycle of IC and two months after completion of CCRT for assessment of tumor response. Subsequent clinical follow-up was 3 monthly in the first 2 years, then 6 monthly afterwards. CT scan and Nasopharyngoscopy with biopsy were performed whenever persistent disease or local recurrence was suspected during follow-up period. Chest X-ray was annually performed or when it was clinically indicated.

**Toxicity evaluation:**

IC related toxicities were recorded according to the National Cancer Institute Common Toxicity Criteria version 2.0 [19]. Acute and chronic radiation related toxicities were graded according to the acute and chronic Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) [20].

**Tumor response:**

Tumor response was defined according to the WHO criteria [21].

**Survival and patterns of failure:**

Survival was estimated from the date of first treatment day to death or last follow-up visit. PFS was estimated from the date of first treatment day to first evidence of disease progression. Early failure means failure to achieve local and/or regional control at the first time of assessment after chemoradiation. Delayed failure means failure during the course of follow-up. Patients who rendered in complete response after neck dissection was considered disease free unless they developed delayed failure during follow-up.
RESULTS

The demographic baseline patients, and disease characteristics of the 36 eligible patients with locally advanced NPC including age, sex, performance status, WHO classification and AJCC/UICC staging are detailed in Table (1).

Treatment compliance and toxicity:

A- Induction chemotherapy:

Twenty nine patients (80%) received 3 cycles of IC, of which two patients shifted to paclitaxel/cisplatin because of low level of creatinine clearance after the second cycle of chemotherapy. Seven patients received only 2 cycles of chemotherapy because they have either stable or progressive disease. Nine patients (25%) have a 25% reduction of chemotherapy doses in subsequent cycles because of developing G 3/4 neutropenia or thrombocytopenia. Three patients (8%) developed grade 2 peripheral neuropathy after the third cycle. Fourteen patients (42%) developed at least one grade 3 or 4 toxicity. Grade 3/4 neutropenia, mucositis and vomiting, the most pronouncing toxicities during IC were recorded in 25%, 22% and 20% of patients respectively (Table 2).

B- Concomitant chemoradiation:

Out of thirty six patients, twenty patients (56%) completed 3 cycles of cisplatin during radiation, and 11 patients (31%) received 2 cycles of chemotherapy and the remaining five patients received only one cycle of chemotherapy because of treatment intolerability. Five patients (14%) received carboplatin instead of cisplatin, 2 because of peripheral neuropathy and 3 patients because of low Cr Cl. Thirty two patients (89%) completed successfully the basic course of external irradiation and 4 patients received suboptimal doses (46, 52, 60 and 60Gy respectively) because of disease progression in two patients and treatment intolerability in the remaining 2 patients. The median overall treatment time for radiotherapy was 52 days (range from 40 days to 62 days). Twenty one patients (58%) developed at least one grade 3 or 4 toxicity. Grade 3 and 4 mucositis, dermatitis, anemia and vomiting, the most severe toxicities during CCRT, were developed in 36%, 28%, 14% and 14% of patients respectively (Table 2). No serious late radiation effects such as blindness, myelopathy or soft tissue necrosis have occurred. All the patients have variable degree of submental edema. Twelve patients (33%) have grade 3 chronic xerostomia. Two patients (6%) have clinical hypothyroidism. Five patients (14%) experienced hearing impairment during follow-up.

Response:

After 2 cycles of IC, 29 patients (80%) achieved objective response [CR in 7 patients (19%) and PR in 22 patients (61%)]. Five patients (14%) have stable disease and two patients (6%) have progressive disease. At the end of treatment, 32 patients (89%) achieved objective response [CR in 25 patients (70%) and PR in 7 patients (19%)]. Of the 7 patients who have partial response; three have only residual neck disease that mandated neck dissection to render disease free, and three patients have residual disease in the nasopharynx that proved positive by biopsy, and one patient have residual nasopharyngeal and neck disease. This means that 28 patients (78%) rendered disease free after chemoradiation and neck dissection. Four patients failed to achieve objective response at the end of treatment (2 have stable and 2 have progressive disease). Of interest, 8 patients failed to achieve complete response at the nasopharynx, 7 patients had originally T4 disease and one patient had originally T3 disease. Table (3) shows the clinical response after induction chemotherapy and at the end of treatment.
A correlation between the complete response (25 patients) achieved at the end of treatment and the different prognostic factors (Table 4) revealed that there was a tendency for better results for patients with smaller tumor volume (stage III), WHO type III pathology, and good performance status (0&1). However, the differences were statistically insignificant.

Survival and progression free survival:

The median follow-up duration was 34 months (range from 7 to 48 months). The actuarial 3 years survival was 68%, [95% CI 53% & 84%]. The actuarial 3 year PFS was 66%, [95% CI 50% & 82%] (Fig. 1). A correlation between the survival and PFS and the different prognostic factors revealed that survival and PFS were significantly better only for patients with smaller tumor volume (stage III), compared with patients with stage IV \((p=0.001)\) (Fig. 2A,B).

Pattern of treatment failure:

The details of patterns of failure were shown in Table (5). A total of 15 patients (41%) have treatment failure, 11 patients (30%) have an early failure, three of them have residual neck disease at the completion of the treatment and rendered disease free after neck dissection, and 4 patients (11%) have delayed failure. Thirteen patients (36%) have elements of local and/or regional failure and 5 patients (14%) have an element of distant metastasis.
NPC is distinguished by relative radiosensitivity and chemosensitivity. Several phase II trials of IC followed by cisplatin-based CCRT have been published with promising results [22-29]. Various cisplatin-based chemotherapeutic regimens have been utilized for induction therapy e.g. cisplatin, epirubicin, and continuous infusional fluorouracil (ECF) [22], cisplatin, fluorouracil, leucovorin and interferon-α 2b [23], carboplatin and paclitaxel [24]. Cisplatin and 5 FU [25,26] cisplatin, epirubicin, and paclitaxel [27], cisplatin and epirubicin [28] and cisplatin and gemcitabine [29].

In the present study, all the patients have high risk locally advanced disease, 56% have T4 disease and 86% have N2/3 disease. The objective response rate was 80% after IC (CR 3/6 (50%) 22/30 (73%) 0.3). V arious cisplatin-based chemotherapeutic regimens have been utilized for induction therapy e.g. cisplatin, epirubicin, and continuous infusional fluorouracil (ECF) [22], cisplatin, fluorouracil, leucovorin and interferon-α 2b [23], carboplatin and paclitaxel [24]. Cisplatin and 5 FU [25,26] cisplatin, epirubicin, and paclitaxel [27], cisplatin and epirubicin [28] and cisplatin and gemcitabine [29].

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Table (4): Prognostic factors in relation to complete response at the end of treatment.

<table>
<thead>
<tr>
<th>Category</th>
<th>Objective response</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 (6)</td>
<td>3/6 (50%)</td>
<td>0.3</td>
</tr>
<tr>
<td>&gt;30 (30)</td>
<td>22/30 (73%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (22)</td>
<td>16/22 (72%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Females (14)</td>
<td>9/14 (64%)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III (14)</td>
<td>11/14 (79%)</td>
<td>0.2</td>
</tr>
<tr>
<td>IV (22)</td>
<td>14/22 (64%)</td>
<td></td>
</tr>
<tr>
<td>WHO Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II (11)</td>
<td>6/11 (55%)</td>
<td>0.2</td>
</tr>
<tr>
<td>III (25)</td>
<td>19/25 (76%)</td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0&amp;1 (33)</td>
<td>24/33 (73%)</td>
<td>0.4</td>
</tr>
<tr>
<td>2 (3)</td>
<td>1/3 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

* Those patients rendered disease free after neck dissection.

Table (5): Pattern of treatment failure.

<table>
<thead>
<tr>
<th>Failure</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local failure only</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Regional failure only</td>
<td>3 (8%)*</td>
</tr>
<tr>
<td>Locoregional failure only</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Distant metastasis only</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Distant metastasis + local/regional failure</td>
<td>3 (8%)</td>
</tr>
</tbody>
</table>

DISCUSSION

NPC is distinguished by relative radiosensitivity and chemosensitivity. Several phase II trials of IC followed by cisplatin-based CCRT have been published with promising results [22-29]. Various cisplatin-based chemotherapeutic regimens have been utilized for induction therapy e.g. cisplatin, epirubicin, and continuous infusional fluorouracil (ECF) [22], cisplatin, fluorouracil, leucovorin and interferon-α 2b [23], carboplatin and paclitaxel [24]. Cisplatin and 5 FU [25,26] cisplatin, epirubicin, and paclitaxel [27], cisplatin and epirubicin [28] and cisplatin and gemcitabine [29].

In the present study, all the patients have high risk locally advanced disease, 56% have T4 disease and 86% have N2/3 disease. The objective response rate was 80% after IC.
19% and PR 61%). After CCRT and neck dissection, CR rate was achieved in 78% of the patients. These results compared favorably to the results reported by other similarly designed phase II trials [22,26-28]. In these trials, the objective response rate after IC was achieved in 79%-86% of patients (CR from 6%-15%) and at the end of the treatment, CR rate ranged from 56% to 80%. However, other investigators reported objective response rate ranging from >90% to 100% after IC and at the end of treatment [23,29,30]. The drawback in these studies was that only clinical and endoscopic examinations were used to assess response after IC; the inclusion of radiologic imaging would give a more accurate and comprehensive assessment.

In the International Nasopharyngeal Carcinoma Study Group [30] locally advanced NP patients were treated with the combination of cisplatin, epirubicin, and continuous infusion of bleomycin (BEP). Those patients achieved a complete response rate of 47% after IC. The BEP regimen was accompanied by excessive toxicity and 8% treatment related mortality rate. In addition, the response in this trial was reported based on clinical assessment without any imaging assessments. The relatively high locoregional control rate at the end of treatment, in different trials, may be attributed to the greater cytoreduction before starting radiation as a result of better drug delivery to the tumor with still intact vasculature during IC. In addition, 8 patients, in the present study, failed to achieve complete response at the nasopharynx, 7 patients had originally T4 disease and one patient had originally T3 disease. We believed that, the results can be improved more in the future with the different boost techniques using brachytherapy, 3D conformal irradiation or IMRT which provide dose escalation with better dose differentiation between tumor and normal tissues [9,31,32].

The actuarial 3 years survival and PFS, in the present study, were 68% and 66% respectively. Survival and PFS were significantly better for patients with smaller tumor volume (stage III), compared with patients with stage IV. Our results compared favorably to other phase II similarly designed studies [25-29]. In contrary, Rischin et al. [22] reported an excellent 4-year overall survival of 90% and the 4-year PFS rate was 81%. However, in Rischin et al. trial, only 40% of patients were of stage IV according to the new staging (UICC criteria, ed. 5, 1997). The study by Lin et al. [6] using concurrent cisplatin plus 5-FU and radiation achieved significant benefit in both PFS and overall survival over radiation alone. The magnitude of gain in the 5-year overall survival rate amounted to 18% (72% Vs. 54%). However, only 29% of patients have stage IV disease according to (UICC criteria, ed 5, 1997). The trial by Chan et al. [7] using concurrent cisplatin and radiation showed that the gain in 5-year PFS was 8% (60% Vs. 52%) and the gain in overall survival was 11% (70% Vs. 59%). However, in Chan et al., trial, only 29% of patients have T3/T4 disease, and 26% have stage II disease in chemoradiation arm.

The primary rationale for IC in nasopharyngeal cancer has been to decrease the risk of developing distant metastases. Five patients (14%) have an element of distant metastasis. In CCRT trials, despite achievement of excellent locoregional control, the incidence of distant metastasis remained as high as 36% [6,7,9-11]. The higher incidence of distant metastasis in CCRT strategy may be explained by the fact that systemic levels of the drugs, which were usually suboptimal, during radiation, were not sufficient to control micrometastatic disease. Improved control of distant disease could be achieved by eradicating micrometastatic disease through systemic drug delivery before the local treatment.

The induction therapy and chemoradiation were well tolerated as 80% of patients completed 3 cycles of IC. The IC did not interfere with the delivery of subsequent treatment as 87% of patients completed successfully the basic course of external irradiation concomitant with at least 2 cycles of chemotherapy. One advantage of induction compared with adjuvant chemotherapy is the greater ability to administer full-dose chemotherapy as planned. In the present trial, only 9 patients have 25% reduction of chemotherapy dose because of G3/4 toxicity. In IGS trial [1], only 55% of patients received all three planned cycles of adjuvant chemotherapy and 33% did not receive any adjuvant chemoradiotherapy. Of major concern in our study was the incidence of peripheral neuropathy because of the overlapping toxicities between paclitaxel and cisplatin, 3 patients (8%) developed grade 2 peripheral neuropathy after the third cycle which was compared favorably to other studies.
utilizing platinum compounds and taxanes. Fountzilas et al. [27] recorded 13% incidence of grade 1/2 peripheral neuropathy after IC of cisplatin, epirubicin and paclitaxel. During CCRT, we preferred to use cisplatin 20mg/m²/day over 5 days because high-dose cisplatin (100mg/m² on one day every 3 weeks) infusion often causes severe emesis with subsequent treatment interruption. The IC did not add to the morbidity of subsequent chemoradiation. Lin et al. [6] reported in their randomized trial, 45% and 30.5% incidence of G3/4 mucositis and dermatitis respectively in the chemoradiation group. This better treatment tolerability can be explained by the fact that nutrition and nitrogen balance could be improved in these patients due to cytoreduction induced after IC which may ameliorate the severity of acute toxicity during CCRT.

Conclusions: IC followed by CCRT treatment program is feasible, tolerable and safe. This strategy improved local control and distant disease control. Although this combined treatment program have failed to improve survival rates over the historical result of CCRT trials, randomized trials on a larger number of patients with longer follow-up are required before getting solid conclusions.

REFERENCES


