Concurrent Chemoradiotherapy for Locoregionally Advanced Nasopharyngeal Carcinoma: is Intergroup Study 0099 Feasible in Japanese Patients?

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Background: Since the publication of the significant results of the Intergroup Study 0099 (IGS) in 1998, radical radiation therapy (RT) with concurrent and adjuvant chemotherapy has become the standard care for patients with locoregionally advanced nasopharyngeal carcinoma (NPC) in the United States. An update in 2001 further strengthened the findings of the interim analysis, however, no prospective randomized trials other than this study have confirmed the feasibility of this strategy.

Methods: We attempted to adopt the same combined modality treatment for three consecutive Japanese patients with locoregionally advanced NPC to evaluate its toxicity and efficacy. They were planned to receive radical RT concurrently with cisplatin every 3 weeks, and to receive adjuvant chemotherapy thereafter.

Results: The hematological toxicities were mild and well tolerated in all three patients; however, they all experienced severe (grade 3 and/or 4) skin reactions, pharyngitis and dysphagia, which led to the discontinuation of the planned chemotherapy. They were able to complete RT without treatment breaks, and all three patients achieved complete response at the end of treatment. However, two experienced recurrences after 8 and 10 months, respectively, and died of their disease.

Conclusions: Due to these severe acute adverse events, poor compliance and unsatisfactory outcomes, we have concluded that physicians should be careful in applying the concurrent chemoradiotherapy protocol employed by the IGS for locoregionally advanced Japanese NPC patients.

Key words: NPC – Intergroup study 0099 – concurrent chemoradiotherapy – feasibility

INTRODUCTION

Radical radiation therapy (RT) remains the primary treatment of choice for patients with non-metastatic nasopharyngeal carcinoma (NPC). However, the treatment outcome of stage III and IVA/B (according to UICC–TNM 1997) NPC by conventional radiotherapy is not satisfactory. NPC is not only a radiosensitive tumor but is also chemo-sensitive and has shown high response rates to various chemotherapeutic agents in many studies (1–4). Thus, sequential chemoradiotherapy in the form of neoadjuvant chemotherapy or adjuvant setting was tested in various prospective randomized trials, but both strategies failed to improve overall survival compared with RT alone (5–8).

In contrast, Intergroup Study 0099 (IGS), coordinated by the Southwest Oncology Group (SWOG), has demonstrated significant results (9). The Intergroup trial used concurrent and adjuvant chemotherapy with RT, and did show improved overall survival favoring the combined modality arm. Interim analysis showed that 3-year overall survival was 76% in the experimental arm and 46% in the RT alone arm, with fewer locoregional failures and distant metastases in the combined modality arm. An update in 2001 reported corresponding overall survival rates at 5 years of 67 and 37%, respectively (10). As a consequence, the administration of concurrent chemoradiotherapy has become the standard care for locoregionally advanced NPC in the USA. However, there are many criticisms...
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in extrapolating the findings of this study to Asian countries, where NPC is endemic. Such comments include reference to differences in histologic subtypes, inferior outcomes in the control arm and racial composition.

We attempted to adopt the same combined modality treatment for patients with locoregionally advanced NPC. However, all three consecutive patients treated at our institution experienced severe acute adverse events and were not able to complete the combined modality treatment regimen.

PATIENTS AND METHODS

PATIENT CHARACTERISTICS

Three consecutive patients with biopsy-proven stage III and IV NPC without evidence of distant metastasis (M0) were the subjects of this study. The patients were required to have the following laboratory values: WBC count >3000/μl, platelet count >100 000/μl, serum creatinine <1.5 mg/dl and/or creatinine clearance >60 ml/min. The patients were also required to have a Karnofsky Performance status of at least 80. All three patients underwent a complete history, physical examination, complete blood counts, screening blood tests of hepatic and renal function, and 3 consecutive days of 24 hour creatinine clearance. The disease evaluation included a chest radiograph, bone scintigraphy, computed tomography (CT) of the head and neck, chest and abdomen, magnetic resonance imaging (MRI) of the nasopharynx and base of skull and fiberoptic endoscopy and biopsy of the nasopharynx. The patients were staged according to the 1997 UICC–TNM staging system. The patient characteristics are shown in Table 1. Informed consent was provided according to the Declaration of Helsinki.

CHEMOTHERAPY

The same chemotherapy regimen reported by the IGS was adopted, consisting of cisplatin (CDDP) 100 mg/m² on days 1, 22 and 43 of RT and CDDP 80 mg/m² for 1 day and 5-fluorouracil (5-FU) 1000 mg/m² for 4 days starting on days 71, 99 and 127. All patients received adequate hydration and serotonin antagonist against emesis during CDDP administration.

RADIATION THERAPY

CT-based treatment planning was used to assess the extent of the primary tumor, as well as the neck nodes. The treatment volume included the primary tumor site and the neck nodes above the clavicle. The nasopharynx and the upper neck were treated with two opposed lateral fields. A separate anterior supraclavicular field was used to irradiate the low neck and supraclavicular fossa. Dose distribution of Case 1 is shown in Fig. 1. The patients were treated with a combination of 4 and 10 MV photons to achieve dose homogeneity. The fractional daily dose was 2 Gy (gray) with a planned total dose of 70 Gy.

RESPONSE AND TOXICITY EVALUATION

The response assessment included physical examination, fiberoptic endoscopy and CT and/or MRI of the nasopharynx and neck. The responses were classified as follows: CR (complete response), disappearance of all disease; PR (partial response), decrease in 50% or more of all measurable lesions; NC (no change), <50% reduction in the initial tumor size. Acute toxicities were graded according to the National Cancer Institute common toxicity criteria.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>TNM</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>58</td>
<td>Male</td>
<td>T2aN3bM0</td>
<td>WHO III</td>
</tr>
<tr>
<td>Case 2</td>
<td>43</td>
<td>Male</td>
<td>T1N2M0</td>
<td>WHO III</td>
</tr>
<tr>
<td>Case 3</td>
<td>59</td>
<td>Male</td>
<td>T1N3aM0</td>
<td>WHO II</td>
</tr>
</tbody>
</table>

Figure 1. Dose distribution of Case 1. (Top) At the level of nasopharynx. (Bottom) At the level of hyoid bone.
RESULTS
None of the three patients was able to complete the planned combined modality. Case 1 received 100 mg/m² of CDDP on days 1 and 28, and the others received CDDP on only day 1 of treatment. All the patients declined to receive the planned adjuvant chemotherapy because of severe acute toxicities. RT was delivered without treatment breaks to all three patients, and the total irradiation doses were 60, 68 and 70 Gy, respectively. The acute toxicity profiles, other than hematological adverse events, are shown in Table 2. Although Case 3 experienced grade 3 leukopenia, the other hematological toxicities were well tolerated (grades 0–2). However, all patients experienced grade 3 or 4 skin reactions, pharyngitis and dysphagia, which led to the discontinuation of the planned treatment (Fig. 2). There was no treatment-related death. At the end of the treatment, all patients achieved CR, however, Case 1 developed distant metastasis (lung and bone) at 10 months, and Case 2 experienced local recurrence (orbit, extra-field) at 8 months. Both patients died of their disease, and only Case 3 was alive without disease at last follow-up.

DISCUSSION
Patients with locoregionally advanced NPC have traditionally been treated solely with conventional RT; however, many develop local and/or distant failures and the long term survival rates are not satisfactory. In an attempt to improve the treatment outcomes, several groups have incorporated chemotherapy adjuvantly, neoadjuvantly or concurrently with RT in randomized controlled trials (5–12). However, the majority of these trials failed to show any significant survival benefit. The results of a meta-analysis of 1528 patients from six randomized trials (5–12) demonstrated that the addition of chemotherapy to radical RT for locoregionally advanced NPC increased both disease free/progression free and overall survival by between 19 and 40% at 2–4 years after treatment, depending on the endpoint of interest (13). However, this meta-analysis was not based upon individual patient data, and all but one of the six (Intergroup Study 0099) examined the role of neoadjuvant chemotherapy. Furthermore, one study administered chemotherapy both adjuvantly and neoadjuvantly, and of the remaining four randomized trials evaluating the efficacy of neoadjuvant chemotherapy, two showed the survival benefit of the experimental arm, but the other two did not. Thus, this meta-analysis did not demonstrate that we should administer concurrent chemoradiotherapy for locoregionally advanced NPC in the setting of clinical practice.

With respect to the timing of chemotherapy and radiotherapy, several researchers have examined the efficacy of alternating schedule (14,15). On the other hand, in an attempt to improve the local control rates for patients with anatomically advanced disease, some investigators have attempted to deliver higher radiation doses by the introduction of endocavitary brachytherapy, hyperfractionated RT and intensity modulated RT (16,17). Both of these studies demonstrated promising results, however, no confirmatory phase III trials have been reported.

Concurrent chemoradiotherapy with adjuvant chemotherapy has become standard practice in the USA following the publications of excellent results by the IGS. Recently, a Taiwan group has also demonstrated that concurrent chemoradiotherapy, consisting of CDDP and 5-FU as a continuous infusion, significantly improved both overall survival and progression free survival (PFS) with acceptable toxicities in NPC endemic areas (12). This is the only phase III trial to demonstrate a positive effect of concurrent chemoradiotherapy without any adjuvant or neoadjuvant chemotherapies. Several groups have evaluated the efficacy of concurrent chemoradiotherapy and adjuvant chemotherapy in phase II trials and have also demonstrated promising outcomes (18–21). Chan et al. (11) compared concurrent chemoradiotherapy with RT alone in a randomized phase III trial. They administered 40 mg/m²/w of CDDP concurrently with radical RT (66 Gy/6.5 w) in the experimental arm. At a median follow-up of 2.71 years, although the subgroup analysis demonstrated that the PFS of patients with advanced tumor and node stages was significantly prolonged in the experimental arm, the 2-year PFS rates were not statistically different between the treatment groups. Moreover, several criticisms have been reported with regard to

Table 2. Acute adverse event, maximum grade observed for each patient

<table>
<thead>
<tr>
<th>Event</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>2 (–18.1%)</td>
<td>2 (–12.9%)</td>
<td>2 (–12.2%)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 2. Photograph of skin reaction observed at 54 Gy in Case 1. We could observe moist desquamation at bilateral supraclavicular fossae and middle of the neck (grade 3). He developed bleeding thereafter.
the IGS. A Canadian group examined the treatment outcome of their patients treated with RT alone and compared this with the IGS (22). They concluded that the surprisingly poor outcome of the control arm of IGS may have resulted by chance, and that a randomized trial is essential to establish the role of combined chemotherapy and RT.

A Singapore group explored the feasibility and efficacy of a concurrent chemoradiotherapy protocol, similar to that used in the IGS, and concluded that it was feasible in the Asian context (21). Contrarily, Chua et al. (23) evaluated the toxicity and efficacy of the IGS protocol in 47 Chinese patients with stage III and IV NPC, and compared them with a matched control treated solely with RT. They indicated that concurrent chemoradiotherapy improves locoregional control, but failed to detect any impact on distant failure and survival, and suggested that caution should be exercised in extrapolating the findings of the IGS to Chinese patients. Furthermore, Baron-Hay et al. (24) reported a patient treated with this protocol that subsequently developed severe life-threatening laryngeal necrosis. In our study, the patients could not accomplish their planned treatment due to severe acute adverse events, and two out of the three experienced recurrences and died of their disease. This high recurrence rate outside of the irradiated field would probably be attributable to the relatively low intensity of systemic chemotherapy.

We conclude that the concurrent chemoradiotherapy protocol employed by the IGS should be applied carefully for locoregionally advanced Japanese NPC patients because of its severe acute adverse events, poor compliance and unsatisfactory outcome. It is essential to carry out a confirmatory randomized trial to discover whether or not the IGS protocol is appropriate for patients with locoregionally advanced NPC.

References


