CONCURRENT CHEMOIRRADIATION WITH CISPLATIN FOLLOWED BY ADJUVANT CHEMOTHERAPY WITH IFOSFAMIDE, 5-FLUOROURACIL, AND LEUCOVORIN FOR STAGE IV NASOPHARYNGEAL CARCINOMA


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Abstract: Background. To evaluate the toxicity and efficacy of concurrent chemoirradiation with cisplatin followed by adjuvant ifosfamide, 5-fluorouracil and leucovorin in patients with stage IVb nasopharyngeal carcinoma (NPC).

Patients and Methods. Between October 1998 and August 2001, 35 Chinese patients with stage IVb NPC (N3a:12, N3b:23) were treated with concurrent chemoirradiation using cisplatin 100 mg/m² on days 1, 22, and 43 of radiotherapy, followed by adjuvant chemotherapy with 1.4 g/m² ifosfamide, 450 mg/m² 5-fluorouracil, and 20 mg/m² leucovorin daily for 5 days and repeated every 3 weeks for three cycles. Radiotherapy was given using standard fractionation at 2 Gy/day to a total of 68 Gy to the nasopharynx and 66 Gy to the neck.

Results. All patients completed the prescribed radiotherapy. Twenty-three patients (66%) completed all scheduled cycles of chemotherapy. The compliance rate for concurrent and adjuvant chemotherapy was 71% and 80%, respectively. Grade 3 mucositis occurred in 37%, and grade 3 dermatitis occurred in 11.5% during radiotherapy. Grade 3 neutropenia occurred in 17% during concurrent chemotherapy, and grade 3–4 neutropenia occurred in 48.5% during adjuvant chemotherapy. There were no treatment-related deaths. With a median follow-up of 31 months, the 3-year relapse-free rate was 60%, and the 3-year overall survival rate was 74%. Locoregional control was excellent, with a 3-year local and nodal relapse-free rate of 91% and 83%, respectively. Eleven patients (31%) had developed distant metastases, and the 3-year distant metastasis-free rate was 66%.

Conclusions. The chemotherapy regimen tested is practical with an acceptable compliance rate. Despite having a more advanced stage disease, the observed outcome of our patients seems to be comparable with other series using platinum-based adjuvant chemotherapy. Further investigation to confirm the benefit of using the study regimen in advanced stage NPC is warranted. © 2004 Wiley Periodicals, Inc. Head Neck 26: 118–126, 2004

Keywords: nasopharyngeal carcinoma; chemoirradiation; adjuvant chemotherapy; cisplatin; ifosfamide

Undifferentiated carcinoma of the nasopharynx (NPC) is highly sensitive to chemotherapy and radiation. Unlike other squamous cell carcinoma of the head and neck, both the distant metastases and locoregional recurrence are major failure patterns in advanced-stage NPC. To improve the treatment outcome in NPC, chemotherapy has...
been combined with radiation using different schedules and sequencing for locoregionally advanced disease. The first randomized trial that demonstrated survival benefit with the addition of chemotherapy in advanced stage NPC was the Intergroup 0099 trial that used concurrent cisplatin during radiotherapy followed by adjuvant chemotherapy with cisplatin and 5-fluorouracil.¹ There are, however, some concerns as to whether the findings of the Intergroup study can be extrapolated to patient groups in Asia where the disease is endemic because of the differences in racial composition and histologic types. There are now ongoing trials in Asian countries with the aim of validating the results of the Intergroup study using an identical or modified chemotherapy protocol.

Our center has adopted the use of chemoirradiation for selected patients with locoregionally advanced NPC since 1997, using a chemotherapy regimen identical to that reported in the Intergroup trial. Our preliminary experience indicates that chemoirradiation improves locoregional control in Chinese patients with advanced-stage NPC, but no significant impact on distant failure and survival was detected.² Chemoirradiation also gave rise to substantial toxicity, with a resultant low chemotherapy completion rate. Compared with the Intergroup study, our patients had a similar compliance rate for chemotherapy concurrent with radiation (completion rate 62% vs 63%) but poorer compliance for adjuvant chemotherapy (completion rate, 40% vs 55%). It is uncertain whether the low compliance rate of adjuvant chemotherapy could account for the lack of survival benefit.

To further improve the treatment outcome in advanced-stage NPC, incorporation of other active chemotherapy regimens in the adjuvant setting may be needed. We have previously reported using a regimen of ifosfamide, 5-fluorouracil, and leucovorin in patients with recurrent and metastatic NPC that were considered resistant or refractory to cisplatin and 5-fluorouracil, and we observed a response rate of 55%.³ The regimen was also well tolerated, even in patients heavily pretreated with platinum chemotherapy. Combining cisplatin and ifosfamide-based chemotherapy as part of chemoirradiation treatment may improve the compliance and treatment outcome in advanced-stage NPC. We therefore conducted a study in which patients with advanced-stage NPC were treated by chemoirradiation with cisplatin followed by adjuvant chemotherapy with ifosfamide, 5-fluorouracil, and leucovorin regimen, and we report here our preliminary results.

PATIENTS AND METHODS

Patient Selection. This was a single-center phase II study testing the efficacy and toxicity of combined chemoirradiation using concurrent cisplatin and adjuvant ifosfamide, 5-fluorouracil, and leucovorin in stage IVb NPC. The main inclusion criteria was N3 disease characterized by nodal size larger than 6 cm and/or presence of lower neck node metastases. Other inclusion criteria were histologically proven NPC, age ≤70, Karnofsky performance score ≥70, adequate hematologic and renal reserve, and absence of distant metastases at diagnosis. Between October 1998 and August 2001, 52 Chinese patients with newly diagnosed stage IVb NPC were referred to us for treatment. All patients were interviewed for study recruitment, with the treatment option of chemoirradiation using the Intergroup study 0099 regimen. Since February 2001, patients with T1–4N2–3 NPC were also given the option of participation in another phase III multicenter study with treatment arms identical to that of Intergroup 0099 study. As a result, 35 patients were recruited into the current study, 9 patients opted for chemoirradiation using the Intergroup regimen, and 8 patients were recruited into the multicenter study (4 random assigned to chemoirradiation and 4 to radiotherapy alone). All 35 patients recruited into this study had a histologic diagnosis of NPC and were staged according to the 1997 AJCC stage classification. Pretreatment assessment included physical examination, complete blood count, renal and liver biochemistry, creatinine clearance, fiberoptic endoscopy, biopsy of the nasopharynx, chest radiograph, CT, and MRI of the nasopharynx and neck. For patients with N3b disease or nodal size ≥8 cm, CT or ultrasonographic examination of the liver and bone scan were also performed. The study protocol was approved by the institutional review board, and all patients gave written informed consent to this study.

Radiotherapy. Radiotherapy was performed using the two-phase treatment techniques as described by Ho.⁴ Phase I treatment used two lateral opposing faciocervical fields to cover the nasopharynx and upper neck in one volume, matched with a single lower anterior cervical field for the lower neck. This was followed by phase II treatment.
using the split-field technique with two lateral and single anterior facial fields for the nasopharynx, matched with an anterior cervical field for the neck. Patients with paranasopharyngal disease and those with residual neck nodes at the end of radiotherapy received an additional boost treatment using a single oblique photon field or electron. A total dose of 40 Gy was delivered to the nasopharynx and neck during phase I treatments, using a dose of 2 Gy/fractions, 5 fractions/week. During phase II treatment, 28 Gy was delivered to the nasopharynx and 26 Gy to the neck. Boost treatment was given with 2 Gy/fraction to a total of 10 Gy. The total dose delivered to the nasopharynx and neck (excluding boost treatment) was 68 Gy and 66 Gy, respectively.

**Chemotherapy.** Patients were scheduled to receive a total of six cycles of chemotherapy. The concurrent part of treatment was identical to the design of Intergroup trial and consisted of cisplatin at a dose of 100 mg/m² given on days 1, 22, and 43 of radiotherapy. Cisplatin was administered as a 4-h intravenous infusion after appropriate hydration. All patients received 5-HT3 antagonists plus dexamethasone as antiemetic premedication. Adjuvant chemotherapy was started 3 weeks after completion of radiotherapy and consisted of ifosfamide at a dose of 1.4 m² administered as a 4-h intravenous infusion after appropriate hydration. Additional doses of 5-HT3 antagonists were given on days 22 and 43 of radiotherapy. Cisplatin was administered as a 4-h intravenous infusion, leucovorin at a dose of 20 mg/m² intravenous bolus, and 5-fluorouracil at a dose of 450 mg/m² administered as a 20-h intravenous infusion, all given daily for 5 days and repeated every three weeks for a total of three cycles. Mesna was given at a dose of 300 mg/m² intravenous bolus at the time of ifosfamide infusion and thereafter at 4-h intervals for a total of four doses. All patients received 5-HT3 antagonist plus dexamethasone as antiemetic premedication. Adjuvant chemotherapy was started 3 weeks after completion of radiotherapy and consisted of ifosfamide at a dose of 1.4 m² administered as a 4-h intravenous infusion, leucovorin at a dose of 20 mg/m² intravenous bolus, and 5-fluorouracil at a dose of 450 mg/m² administered as a 20-h intravenous infusion, all given daily for 5 days and repeated every three weeks for a total of three cycles. Mesna was given at a dose of 300 mg/m² intravenous bolus at the time of ifosfamide infusion and thereafter at 4-h intervals for a total of four doses. All patients received 5-HT3 antagonist plus dexamethasone as antiemetic premedication during adjuvant chemotherapy. Colony-stimulating factors were not used during chemotherapy. A neutrophil count of at least 1.5 × 10⁹/L and a platelet count of at least 100 × 10⁹/L were required before each chemotherapy cycle, and treatment was delayed for 1 week or longer until recovery if the cell counts fell below these levels. Cisplatin was only administered during and up to 1 week after radiotherapy, with further concurrent chemotherapy cycles omitted if they were delayed beyond 1 week after completion of radiotherapy, and adjuvant chemotherapy was given instead. Dose modification was made if the patient had febrile neutropenia or grade 4 neutropenia. For concurrent chemotherapy, cisplatin was initially reduced to 80 mg/m² and further to 60 mg/m² if toxicity persisted. For adjuvant chemotherapy, only ifosfamide was initially reduced to 1.2 g/m² and further to 1 g/m² if toxicity persisted. Chemotherapy was discontinued if the toxicity persisted after two levels of dose reduction.

**Response Assessment and Follow-Up.** Chemotherapy toxicity was evaluated according to NCI common toxicity criteria and radiotherapy toxicity by RTOG criteria. Response to radiotherapy was assessed 2 to 3 months after completion of radiotherapy and included physical examination, nasopharyngoscopy and biopsy, and CT of the nasopharynx and neck. Complete response was defined as complete regression of all evidence of tumor with negative biopsy. Patients with persistent positive nasopharyngeal biopsy specimens 10 weeks after radiotherapy were treated as having residual disease. Patients with residual radiologic abnormality in the nasopharynx but with a negative biopsy specimen were put under close observation with follow-up imaging and biopsy repeated every 4–6 months. Patients with complete response to treatment were followed up every 4–6 weeks in the first year, 2–3 months in the second and third year, and 4–6 months from the fourth year onward. During each follow-up, clinical examinations of the neck and nasopharynx were performed. Chest radiographs were taken annually. Other investigations, including CT and nasopharyngoscopy, were performed if indicated. The median follow-up time was 31 months, with a range of 13–53 months. For the surviving patients, the median follow-up time was 40 months (range, 18–53 months).

**Statistical Analysis.** The following end points were examined: overall survival (OS), relapse-free survival (RFS), local relapse–free survival (LRFS), nodal relapse–free survival (NRF5), and distant metastasis–free survival (DMFS). The survival end points were analyzed and estimated using the product-limit method of Kaplan and Meier. OS was measured from the date of start of radiotherapy to the date of subject death, from any cause, or to the last date the subject was known to be alive. In determining OS, deaths caused by decrease progression or treatment-related complications were both counted. RFS was measured from the date of start of radiotherapy to the date of first documented relapse in any sites, or to date of recent follow-up if no relapse had occurred. Patients who had their relapse successfully sal-
vaged were still counted as treatment failures at time of event occurrence. In patients with residual disease after radiotherapy, RFS was counted as zero. Other end points were similarly measured from the date of the radiotherapy to the time of event occurrence or to the date of recent follow-up if no event had occurred. All patients were included in the analysis on the basis of the intention-to-treat.

### RESULTS

**Treatment Compliance.** Table 1 summarizes the patient and disease characteristics. Twelve patients (34%) had N3a disease, and 23 (66%) had N3b disease. Of the 35 patients entered in the study, 23 (66%) completed all six cycles of chemotherapy. The compliance rates were 71% for the concurrent chemotherapy and 80% for the adjuvant chemotherapy. The median number of chemotherapy cycles received was six, with a range of one to six. For the concurrent chemotherapy, 25 patients (71%) completed three cycles, 9 (26%) had two cycles, and 1 (3%) had one cycle. For the adjuvant chemotherapy, 28 patients (80%) completed three cycles, 1 (3%) had two cycles, and 6 (17%) had none. Reasons for noncompliance of concurrent chemotherapy included cycle delayed beyond 1 week after completion of radiotherapy in nine and patient refusal because of toxicity in one. Reasons for noncompliance of adjuvant chemotherapy included patient refusal because of toxicity in four and prolonged marrow recovery in two, both caused by toxicity of concurrent chemoradiation, and presence of distant failure in one. In addition, about half of the subsequent chemotherapy cycles had to be delayed mostly because of slow marrow recovery, and 85% of patients had at least one cycle of chemotherapy delayed. During concurrent chemotherapy, 53% of patients had one or more cycles delayed, and the percentage increased to 79% during adjuvant chemotherapy. The marrow recovery time after concurrent chemotherapy ranged from ≤3 weeks in 49% of cycles, 3–4 weeks in 25%, 4–5 weeks in 16%, to 5 weeks in 10%. For adjuvant chemotherapy, the marrow recovery time ranged from ≤3 weeks in 41%, 3–2 weeks in 40%, 4–5 weeks in 17%, to >5 weeks in 2%. Consequently, concurrent chemotherapy treatments (excluding the first cycle) were delayed by ≤1 week in 81% of cycles, 1–2 weeks in 14%, and >2 weeks in 5%. For adjuvant chemotherapy, treatments were delayed by ≤week in 80% of cycles, 1–2 weeks in 16%, and >2 weeks in 4%. The number of patient who completed each chemotherapy cycle, number without prolonged marrow recovery after each cycle, and number without delay of chemotherapy during each cycle are listed in Table 2.

**Toxicity.** All 35 patients were evaluable for acute toxicity from concurrent chemoradiation, and 29 patients were evaluable for acute toxicity from
adjuvant chemotherapy. Treatment toxicity was substantial, but there were no treatment-related deaths. For concurrent chemoradiation, the main nonhematologic toxicity was mucositis, with 13 patients (37%), who had grade 3 toxicity develop. Only one patient required insertion of a nasogastric tube for feeding because of mucositis, but radiotherapy was not interrupted. Grade 3 vomiting and dermatitis also each occurred in four patients (11.5%). For hematologic toxicity, grade 3 leukopenia and neutropenia occurred in 14 (40%) and 6 patients (17%), respectively, but there was no grade 4 toxicity. For adjuvant chemotherapy, grade 1 hematuria occurred in four patients (14%), which resolved after an additional dose of mesna. Emesis was mild. Hematologic toxicity was severe: grade 3 and 4 leukopenia occurred in 15 (52%) and 3 (10%) patients, respectively, and grade 3 and 4 neutropenia occurred in 10 (34.5%) and 4 (14%) patients, respectively. No febrile neutropenia occurred during treatment, although one patient had a mild infection in the absence of neutropenia. Chemotherapy was commonly delayed because of slow marrow recovery. Table 3 summarizes the major acute toxicities during treatment.

All 35 patients were evaluable for late toxicity. All patients had varying degrees of xerostomia. Twelve patients (34%) experienced neck fibrosis, including eight with grade 1 toxicity and four with grade 2 toxicity. Hearing impairment was observed in nine patients (26%), with grade 1 toxicity in four, grade 2 in three and grade 3 in two. Three patients (9%) had endocrine complications requir-

### Table 2. Compliance, marrow recovery time, and treatment delay during chemotherapy.

<table>
<thead>
<tr>
<th>Treatment cycle</th>
<th>Received treatment (% of all patients)</th>
<th>No prolonged recovery of marrow (≤3 wk) (% of those treated in each cycle)</th>
<th>No delay of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cycle</td>
<td>35 (100)</td>
<td>24 (68.6)</td>
<td>—</td>
</tr>
<tr>
<td>Second cycle</td>
<td>34 (97.1)</td>
<td>13 (38.2)</td>
<td>23 (67.6)</td>
</tr>
<tr>
<td>Third cycle</td>
<td>25 (71.4)</td>
<td>9 (36)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Fourth cycle</td>
<td>29 (82.9)</td>
<td>13 (44.8)</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>Fifth cycle</td>
<td>29 (82.9)</td>
<td>13 (44.8)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Sixth cycle</td>
<td>28 (80)</td>
<td>9 (32.1)</td>
<td>13 (46.4)</td>
</tr>
</tbody>
</table>

### Table 3. Incidence of acute toxicity during concurrent chemoradiation and adjuvant chemotherapy.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concurrent chemoradiation</strong></td>
<td>(n = 35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (37.1)</td>
<td>10 (28.6)</td>
<td>11 (31.4)</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3 (8.6)</td>
<td>5 (14.3)</td>
<td>13 (37.1)</td>
<td>14 (40)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8 (22.9)</td>
<td>8 (22.9)</td>
<td>13 (37.1)</td>
<td>6 (17.1)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20 (57.1)</td>
<td>13 (37.1)</td>
<td>1 (2.9)</td>
<td>1 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (5.7)</td>
<td>15 (42.9)</td>
<td>14 (40)</td>
<td>4 (11.4)</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>4 (11.5)</td>
<td>18 (51.4)</td>
<td>13 (37.1)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>0</td>
<td>23 (65.7)</td>
<td>8 (22.9)</td>
<td>4 (11.4)</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>34 (97.1)</td>
<td>1 (2.9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| **Adjuvant chemotherapy**     | (n = 29)|         |         |         |         |
| Anemia                        | 6 (20.7)| 8 (27.6)| 11 (37.9)| 3 (10.3)| 1 (3.4)|
| Leukopenia                    | 0       | 3 (10.3)| 8 (27.6)| 15 (51.7)| 3 (10.3)|
| Neutropenia                   | 2 (6.9) | 5 (17.2)| 8 (27.6)| 10 (34.5)| 4 (13.8)|
| Thrombocytopenia              | 25 (86.2)| 3 (10.3)| 1 (3.4)| 0       | 0       |
| Vomiting                      | 13 (44.8)| 12 (41.4)| 4 (13.8)| 0       | 0       |
| Hematuria                     | 25 (86.2)| 4 (13.8)| 0       | 0       | 0       |
ing hormonal replacement: two with hypothyroidism who were asymptomatic and one with low serum testosterone causing impotence. Two patients (6%) without disease relapse had unilateral twelfth nerve palsy. No other major late toxicity such as myelopathy, brain necrosis, or osteoradio-necrosis was observed.

**Treatment Outcome.** The complete response rate after chemoirradiation was 86%. The complete response rate of the primary site and regional disease was 91% and 89%, respectively. Thirteen patients (37%) had residual disease after treatment or had a relapse after the initial complete remission. Of these, one had local failure, one had locoregional failure, six had distant metastases, four had regional and distant failures, and one had locoregional and distant failures. The 3-year RFS rate was 60% (Figure 1). Locoregional control was excellent with a 3-year LRFS rate of 91% and a 3-year NRFS rate of 83%. One patient with local failure alone was successfully salvaged by stereotactic radiosurgery. Another patient with synchronous locoregional failures was also successfully salvaged by transpalatal gold grain implantation and radical neck dissection. Eleven patients (31%) had distant metastases and the 3-year DMFS rate was 66%. The sites of distant metastases were lung in one, liver in two, bone in two liver and bone in three, and multiple in three. Of these 11 patients, 7 received palliative chemotherapy and 4 received palliative radiotherapy; 8 had died of the disease. Twenty-seven patients (77%) are still alive at the time of analysis, including 24 patients who remain disease free. All deaths were due to uncontrolled disease. The estimated 3-year OS rate after treatment was 74% (Figure 2).

**DISCUSSION**

The adjuvant chemotherapy regimen tested in this report is practical in the sense that most patients were able to complete the planned cycles of treatment after chemoirradiation. Failure of completion of adjuvant chemotherapy was mainly due to the toxicity of the preceding concurrent chemoirradiation, and no patients had adjuvant chemotherapy discontinued because of its associated toxicity. In fact, all patients except one were able to complete all three scheduled cycles once adjuvant chemotherapy was started, the latter one had chemotherapy discontinued because of disease progression. The adjuvant chemotherapy regimen was chosen on the basis of our experience, which demonstrated its efficacy when used as a second-line chemotherapy in patients with metastatic NPC. In patients with metastatic and recurrent disease, the regimen was found to be well tolerated and most patients were able to complete the treatment on schedule, even after previous treatment with platinum-based chemotherapy. The 72% compliance rate of concurrent chemotherapy in our study was similar to the reported rates of 62% to 75% in other chemoirradiation series. The 80% compliance rate of adjuvant chemotherapy in our study was, however, better than those reported in other series using adjuvant cisplatin...
and 5-fluorouracil. In the Intergroup trial, the compliance rate of adjuvant chemotherapy was only 55%. In a study by Tan et al., the compliance rate of adjuvant chemotherapy was 63% after chemoirradiation.

In our earlier experience, compliance of adjuvant chemotherapy using cisplatin and 5-fluorouracil was only 40% after chemoirradiation. In that study, the compliance of adjuvant chemotherapy decreased from 66% in the first cycle to 40% in the third cycle compared with a decrease from 83% to 80% in this study. With regard to the hematologic toxicity, the incidence of grade 3 neutropenia during adjuvant chemotherapy was higher in this study, but the incidence of grade 4 neutropenia was similar. The higher incidence of grade 3–4 neutropenia is to be expected because of better treatment compliance. The absence of febrile neutropenia (compared with three episodes in the previous study) may be explained by the relative rapid recovery from nadir during adjuvant chemotherapy in this study. Although we believe the adjuvant chemotherapy tested in this study is better tolerated after concurrent chemoradiation and hence a higher compliance can be achieved, the possibility of investigator bias in ascertaining treatment compliance cannot be excluded. A phase III trial comparing adjuvant chemotherapy using the study regimen and platinum/5-fluorouracil after chemoradiation is therefore needed for definitive conclusion.

In this report, the patients were all Chinese subjects with stage IVb NPC. Stage IVb is characterized by advanced nodal disease, with nodal size exceeding 6 cm in diameter (N3a) or presence of lower neck nodes (N3b). This group represents one with the worst prognosis in nonmetastatic NPC because of a high incidence of distant failure even after successful control of locoregional disease by radiotherapy. Hence, combined modality treatment is essential to improve the survival in this group, which represents an ideal setting for testing the benefit of adjunctive chemotherapy. Many series in which patients were restaged according to the 1997 AJCC stage classification system reported poor outcome in those with nonmetastatic stage IV disease. Cooper et al. observed a 3-year disease-specific survival rate of 59% and a 5-year rate of 39% in 32 patients with stage IV disease treated by radiotherapy alone. Ozyar et al. reported a similar 3-year survival rate of 55% and a 3-year distant metastasis-free rate of 57% in 35 patients with stage IV disease treated by radiotherapy alone. Ma et al. reported the outcome in a larger group of 156 patients with stage IV disease treated by radiotherapy alone, with a 5-year survival rate of 37% and a 5-year distant metastasis-free rate of 51%. These series reported the outcome of patients with both stage IVa and IVb disease, with the former subgroup carrying a better prognosis. The reported outcome of patients with stage IVb disease alone was usually worse. In the study by Heng et al., the 5-year survival rates after radiotherapy alone in 160 patients with stage IVa disease and 94 patients with stage IVb disease were 35% and 28%, respectively. The largest series was reported by Lee et al. with 1083 patients having IVb disease after restaging according to the 1997 AJCC stage classification. Patients in Lee’s series were treated mainly by radiotherapy alone, although a small proportion of patients also received chemotherapy using various chemotherapy regimens and schedules. The observed 10-year disease-specific survival rates for T1N3, T2N3, T3N3, and T4N3 disease were 36%, 29%, 31%, and 15%, respectively. The hazard ratio for distant failure N3 disease was 4.59. Thus the long-term outcome in patients with stage IVb disease after radiotherapy alone is poor mainly because of the high incidence of distant metastases in this group.

On the other hand, patients with stage IV NPC who were treated by chemoirradiation seem to have a better outcome. Cheng et al. reported the outcome of 149 patients with stage II–IV disease after concurrent chemoirradiation followed by adjuvant chemotherapy and observed a 3-year survival rate of 66% in 64 patients with stage IV disease. In 22 patients with stage IVb disease, distant metastasis represents the major failure pattern, which occurred in 40%. We reported earlier our experience of chemoirradiation in advanced-stage NPC using the identical chemotherapy regimen as reported in the Intergroup study 0099 and observed a 3-year survival rate of 62% in 38 patients with stage IV disease. In a recent study by Hong et al., patients with advanced NPC were treated by three cycles of induction chemotherapy with mitomycin, epirubicin, cisplatin, 5-fluorouracil, and leucovorin followed by radiotherapy. The 5-year survival rate for 67 patients with stage IVb disease (59 completed the treatment) was 73%, and the 5-year distant metastasis-free rate for N3a and N3b disease was 79% and 74%, respectively. Our preliminary result of concurrent cisplatin chemoirradiation followed by an adjuvant ifosfamide-based regimen for ad-
advanced-stage NPC is encouraging, and the survival rate seems to be comparable to other chemoradiation series, although our patients had a more advanced stage disease.

Because both locoregional recurrence and distant failure represent major failure patterns in NPC, different treatment strategies may be needed to address the specific failure pattern in a different prognostic group. In patients with predominantly advanced nodal disease, systemic chemotherapy is essential to eradicate the micrometastases. The timing of chemotherapy, the regimens used, and the dose-intensity actually delivered are all important factors that may determine the benefit of combined modality treatment. Results from randomized trials do not support the use of induction chemotherapy and/or adjuvant chemotherapy in advanced-stage NPC.13–17 The first randomized trial that demonstrated survival benefit with the use of chemotherapy was the Intergroup 0099 trial that used concurrent chemotherapy followed by adjuvant chemotherapy in advanced-stage NPC.1 In another randomized trial that used concurrent chemotherapy using weekly cisplatin without any adjuvant chemotherapy in patients with advanced nodal disease, no significant difference in progression-free survival can be demonstrated.18 A recent randomized trial that used two cycles of cisplatin and 5-fluorouracil concurrent with radiotherapy but without adjuvant chemotherapy also showed improved survival compared with radiotherapy alone.19 Thus, randomized trials that used sequential chemoradiation failed to show any improvement in overall survival, whereas two of three trials using concurrent chemoradiation with or without adjuvant chemotherapy demonstrated a major improvement in overall survival. Although it is likely that concurrent chemotherapy plays the major role in improving the treatment outcome, the role of adjuvant chemotherapy after concurrent chemoradiation is uncertain. Future studies should explore the role of adjuvant chemotherapy after concurrent chemoradiation in advanced-stage NPC.

In conclusion, the observed outcome of patients in this study treated by concurrent chemoradiation using cisplatin followed by adjuvant chemotherapy with ifosfamide, 5-fluorouracil, and leucovorin is encouraging. The survival rate seems to be comparable to other reported series using platinum-based concurrent chemoradiation and adjuvant chemotherapy, despite the fact that our patients had a more advanced stage of disease.

In view of the good compliance and encouraging results, a further phase III study to confirm the benefits of the study regimen in advanced stage NPC is warranted.

REFERENCES