Chemotherapy in Advanced Nasopharyngeal Cancer

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Chemotherapy is an integral part of treatment for patients with nasopharyngeal carcinoma. Chemotherapy can achieve long-term survival rates of up to 15% to 20%, even in patients with recurrent or metastatic disease. In

Introduction

Nasopharyngeal carcinoma is a malignant tumor with unique features that make it pathologically, epidemiologically, and clinically distinct from other head and neck cancers. There is no clear association with tobacco or alcohol use in most cases of nasopharyngeal cancer (World Health Organization [WHO] grades II and III). Patients with nasopharyngeal carcinoma have a higher incidence of nodal involvement and bilateral nodal disease at presentation, and overall (80% to 90%) nodal metastasis, as compared with patients with other malignancies of the head and neck. In addition, patients with nasopharyngeal carcinoma have a higher overall incidence of systemic metastasis than patients with tumors in other head and neck sites.

In the United States and Europe, the incidence of nasopharyngeal cancer ranges from 0.5 to 2 cases per 100,000 people.[1] In some areas of the world, namely, southern China, Southeast Asia, North Africa, the Middle East, Alaska, and Greenland,[1-5] nasopharyngeal cancer is more common. In these areas, incidence may be as high as 25 to 50 per 100,000 people,[2] and the pathology is mostly of the undifferentiated variety. The Epstein-Barr virus is more strongly associated with nasopharyngeal carcinoma in areas of higher prevalence and in patients whose tumors are WHO grades II and III than in less aggressive grades and in areas of lower incidence.

Nasopharyngeal carcinoma affects men more often than women, with a male-to-female ratio of 3–3.5:1.[1,6] The incidence of the disease begins to rise at age 20 years and starts to decline at age 60 years, with a median age of incidence of 40 to 50 years.

Treatment Overview

Nasopharyngeal carcinomas respond to radiation therapy (Table 1[7-23]) as well as chemotherapy (Tables 2[24-38] and 3[25,28,30,39-50]). Because nasopharyngeal cancer responds so well to radiotherapy, and in light of the sensitive location of the primary disease and the often advanced stage at presentation, surgery is often unnecessary or impractical. However, for persistent or recurrent disease in regional nodes, surgery is the treatment of choice in most cases.

Radiotherapy has been the traditional, standard form of therapy for all patients with local and locoregional disease. Marcial et al[12] reported complete local clearance of nasopharyngeal carcinoma in 96% of patients with T1 disease treated with radiotherapy, 88% of those with T2, 81% of those with T3, and 74% of those with T4. Complete clearance rates in patients with N1-3 disease who received irradiation ranged from 93% to 71%. The 5-year survival rate of these patients with nodal involvement was only 40%; overall 5-year survival rates of patients with all stages of nasopharyngeal carcinoma treated with radiotherapy, reported by various investigators from all over the world, have ranged from 24% to 62% (Table 1).

Qin et al[18] reviewed the survival rates of 1,379 patients with advanced nasopharyngeal carcinoma treated with radiotherapy. The majority of patients had either stage III (n = 417) or stage IV cancer (n = 647). These investigators reported that the 5, 10-, and 20-year survival rates of patients with stage III cancers treated with radiotherapy alone were 46%, 29%, and 17%, respectively. The 5-, 10-, and 20-year survival rates of stage IV patients treated with irradiation were 29%, 21%, and 8%, respectively. Overall, the 5-year survival rate of nasopharyngeal carcinoma patients with stage IV disease treated with radiotherapy alone was less than 30%, regardless of country of origin or histopathology.

Locoregional recurrences occur in 40% to 80% of patients, and distant recurrences in 15% to 50% of patients. The usual radiation dose is 65 to 75 Gy in 1.8- to 2.0-Gy fractions, 5 days a week. This dose
is crucial for achieving complete locoregional control and 5-year survival.[18] In a nonrandomized trial reported by Wang,[51] the local control rate improved significantly with accelerated hyperfractionated radiotherapy, as compared with once-daily radiotherapy. The improved local control rates occurred in patients with N2-3 disease and among both males and females.

Despite the high initial response rate and good local control achieved with radiotherapy in patients with locally advanced stage III and IV nasopharyngeal carcinoma, the 5- and 10-year survival rates were poor and unacceptable. Options for patients who experience local and/or regional failure include reirradiation and, occasionally, surgical resection; the latter is especially appropriate for patients with involvement of regional lymph nodes only.[52] The majority of patients with recurrent disease, and all patients with metastatic disease, should be treated with systemic chemotherapy for palliation.

**Chemotherapy**

Nasopharyngeal carcinomas are highly sensitive to chemotherapy (Tables 2 and 3). Single agents identified as being active in this disease include methotrexate, bleomycin (Blenoxane), doxorubicin, cisplatin (Platinol), carboplatin (Paraplatin), and, more recently, paclitaxel (Taxol), and to a lesser extent, fluorouracil (5-FU) and the vinca alkaloids. For patients with head and neck cancers in general, and especially for those with nasopharyngeal carcinoma, combination chemotherapeutic regimens are more active than single drugs, and cisplatin-based combinations are more active than non-cisplatin-based combinations.[24-26]

The combination most widely used in these patients is cisplatin plus a 5-FU infusion. The regimen is easy to administer and well tolerated by most patients. Fluorouracil is given at a dose of 1,000 mg/m²/d as a 4- to 5-day continuous infusion, and cisplatin is given at a dose of 80 to 100 mg/m² on the first day of treatment.[53,54] The course is repeated every 3 to 4 weeks.

**Chemotherapy for Recurrent or Metastatic Disease**

Patients with nasopharyngeal carcinoma who present with metastatic disease and those whose cancers recur after initial curative treatment and who have received further local treatment with surgery and/or reirradiation should be treated with systemic chemotherapy for palliative purposes. Because of the rarity of this disease, especially in western countries, all reported chemotherapy trials for recurrent/metastatic nasopharyngeal carcinoma are phase II studies (Table 2). Since 1980, the success of cisplatin-based combinations in patients with head and neck cancers has made these regimens the first choice for the treatment of nasopharyngeal carcinoma (Table 2).[24,26]

As shown in Table 2, the majority of the cisplatin-based combinations reported consist of cisplatin plus a 5-FU infusion, with or without other agents, such as leucovorin or bleomycin. The overall response rate is between 50% and 65%, but, more importantly, approximately 15% to 20% of treated patients achieve a complete response. From the phase II trial data, it does not seem that the addition of other agents to cisplatin-5-FU infusion produces higher overall or complete response rates. More recently, other active combinations have been investigated using newer active agents, such as paclitaxel[35-37] and ifosfamide (Ifex).[38]

The majority of patients who achieve a complete response to chemotherapy remain alive for more than 2 years, or are even considered cured. No standard duration of further treatment in patients who have achieved a complete response has been reported. It is our opinion that, if a biopsy confirms a complete response after local recurrence, or a computed tomographic (CT) scan or bone scan confirms complete response after nodal or systemic recurrence, an additional four to six courses of chemotherapy may need to be administered. Patients who achieve a complete response need to be followed closely, especially for the first 2 years after completion of chemotherapy.

The important prognostic factors that may influence overall and complete response to chemotherapy in nasopharyngeal carcinoma patients[53,54] are performance status, histopathology (WHO grades I, II, and III), local vs systemic disease, site of the systemic metastasis, bulk of recurrent or metastatic cancers being treated, type of chemotherapy combinations used, and adequacy of treatment given.

**Chemotherapy as Part of Combined-Modality Treatment for Primary Disease**

Because of the high incidence of locoregional failure with radiotherapy alone despite the initial high clearance rate, and because of the high incidence of distant metastasis in nasopharyngeal cancers, combined-modality therapy is a very attractive concept. Chemotherapy can be given neoadjuvantly (induction chemotherapy followed by radiation), concomitantly, or adjuvantly (radiotherapy followed by chemotherapy). The use of more than one of these approaches in sequence has also been
Neoadjuvant (Induction) Chemotherapy

Neoadjuvant chemotherapy was explored in the mid-1970s in patients with locally advanced stage III and IV head and neck cancers of all sites. Most of these patients, including those with nasopharyngeal carcinomas, had inoperable or unresectable disease. High overall and clinical complete response rates to induction chemotherapy were obtained, and the feasibility of sequential induction chemotherapy followed by radiotherapy was established. This led to many phase II studies using the same treatments in patients with locally advanced nasopharyngeal cancers (Table 3).

The factors that may influence response rate and overall survival are stage of the nasopharyngeal carcinoma (especially the N stage), performance status, histopathology, type of chemotherapeutic combination used, number of courses, and adequacy of treatment given. In addition, reports of complete response at the primary site may differ from investigator to investigator, depending on whether the response was evaluated clinically, by CT scan, or by magnetic resonance imaging (MRI). Since the majority of patients initially present with T3 or T4 disease, some abnormalities may still be observed locally when a CT scan or MRI is performed; this can occur even in patients who have repeated negative biopsies of these areas and are considered cured without further treatment.

Factors that may affect survival are disease stage, type of response to chemotherapy (partial vs complete), histopathology, and performance status.

The majority of the neoadjuvant chemotherapy trials mentioned here used cisplatin-based combinations, especially cisplatin plus a 5-FU infusion. In a few trials, leucovorin or bleomycin was added to this combination. These studies demonstrated interesting results, with overall response rates of 80% to 90%. In some trials, up to 66% of the responses were complete. Because of the various prognostic factors that may influence response rate, no determination could be made as to the best possible chemotherapy combination.

Geara et al[46] and Teo et al[48] reported much higher complete response rates to chemotherapy for nodal disease than for primary tumors. Both these investigators used CT scans to evaluate responses. In our experience, both in patients with nasopharyngeal carcinoma and in patients with other head and neck cancers treated with chemotherapy, the complete response rate is usually higher at the primary site than the regional lymph nodes.

When the survival of patients treated with chemotherapy followed by irradiation was compared to historical matched controls receiving radiotherapy alone, the majority of investigators reported significant improvement in overall survival for the combined approach. This was especially true for the administration of adequate doses of two to three courses of cisplatin and 5-FU infusion.

Recently, Teo et al[48] reported on the results of two courses of cisplatin and 5-FU infusion followed by radiotherapy in 209 patients with node-positive, locally advanced nasopharyngeal cancers, compared to similar patients treated with radiotherapy alone during the same period. The chemotherapy group had significantly more bulky nodes, lower cervical and/or supraclavicular nodes, and more advanced overall stages than the nonchemotherapy patients. Unfortunately, the duration of the 5-FU infusion was 3 days, instead of the standard 5 days, and only two courses of chemotherapy were given instead of the usual three courses.

Despite these facts, the addition of chemotherapy to radiation treatment significantly enhanced local control in node-positive nasopharyngeal cancer patients in general, and node-positive, T3 and T4, stage IV patients in particular. The 5-year survival rate among patients with stage IV cancers ranged from 50% to 55% in those who underwent sequential radiotherapy, as compared to less than 30% in those who received radiotherapy only. When evaluating survival in patients with nasopharyngeal carcinoma, a minimum follow-up of 3 years is necessary before any conclusions can be drawn.

Concomitant Chemoradiotherapy

This option is attractive, with the possible advantages of synergy between chemotherapy and radiotherapy, as well as additive effects. Chemoradiotherapy has been investigated in many other solid malignancies; improved disease-free and overall survival rates have been reported for the combined approach, as opposed to radiotherapy alone.

Many phase II trials of concurrent chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma have been reported.[55-65] Several chemotherapeutic agents, especially cisplatin,[67-69] produce synergistic and/or additive effects when used with radiotherapy. One possible advantage of using concomitant cisplatin and radiotherapy in patients with head and neck cancers, as opposed to other agents, such as methotrexate, bleomycin, or 5-FU, is the lack of increased local side effects (especially mucositis).

Most investigators gave standard one-fraction-per-day irradiation. The radiation dose was the same as without chemotherapy, ie, > 6,400 cGy in most cases. When the results of concomitant chemoradiotherapy were compared with those of historical matched control patients, most
investigators reported improvements in local control, disease-free survival, and overall survival with the combined treatment.

Other agents, such as the taxanes and gemcitabine (Gemzar), have been shown to be radiation sensitizers and/or enhancers. These agents, administered concomitantly with radiotherapy, may need to be investigated in the future in patients with nasopharyngeal carcinoma.

In an early study published by the Radiation Therapy Oncology Group (RTOG),[64-66] we reported the results of concomitant treatment with single-agent cisplatin and radiotherapy in 124 patients with locally advanced, inoperable or unresectable stage III (n = 24) or stage IV (n = 100) head and neck cancers; this study population included 28 patients with nasopharyngeal cancers, 27 of whom had stage IV disease. The cisplatin dose was 100 mg/m², given intravenously with hydration and mannitol diuresis, once every 3 weeks, concurrent with standard radiation therapy to a total dose of up to 7,380 cGy. Complete response rates were 70% for all patients and 89% for those with nasopharyngeal cancers.

When the survival of patients with nasopharyngeal cancer was compared with survival of those with tumors of other head and neck sites (all were treated with the same chemoradiotherapy), a significantly higher survival rate was observed in the nasopharyngeal carcinoma patients. In addition, the survival of the nasopharyngeal carcinoma patients treated with concurrent cisplatin and radiotherapy was significantly better than the survival of historical matched controls treated with the same dose of radiotherapy alone.

Even more interesting was the fact that approximately 55% of the patients with cancers of the nasopharynx who had received chemoradiotherapy were still alive 5 years later. No additive local toxicities were observed with chemoradiotherapy when compared to matched historical control patients with head and neck cancers treated with the same dose of radiotherapy alone.

• Adjuvant Chemotherapy—

In patients with locally advanced nasopharyngeal carcinoma, the administration of systemic chemotherapy after radiotherapy may help to consolidate the local control achieved with radiation and reduce the incidence of microscopic systemic metastasis. These beneficial effects of adjuvant chemotherapy may result in improved disease-free and overall survival.

A prospective, randomized trial[70] of radiotherapy followed by vincristine, cyclophosphamide (Cytoxan, Neosar), and doxorubicin that did not show any benefit from the use of adjuvant chemotherapy is discussed below. In another phase II trial,[71] the combination chemotherapy used (5-FU and cisplatin) was too toxic, resulting in high treatment-related mortality. Other reports[72-76] of single-arm studies, however, did show possible benefits of adjuvant chemotherapy in patients with nasopharyngeal carcinoma. Many newer agents, and combinations thereof, may have fewer local mucosal side effects; these may need to be investigated in the future.

Randomized Trials

Five prospective, randomized, phase III trials of adjuvant therapy comparing chemoradiotherapy to the same dose of radiotherapy alone have been reported thus far in patients with locally advanced nasopharyngeal cancers.[70,77-83] Three such studies gave only sequential chemotherapy followed by radiotherapy. In two of these trials, cisplatin was combined with drugs other than a 5-FU infusion. In a trial conducted by the International Nasopharyngeal Cancer Study Group,[77,79] 339 patients were randomized to receive either three courses of induction chemotherapy using the combination of bleomycin, cisplatin, and epirubicin (Ellence) followed by radiation therapy, or radiation therapy alone. In the initial report of this study, induction chemotherapy prolonged disease-free survival but no overall survival difference between the two groups was reported. A recent update of this trial, after a median follow-up of 74 months, confirmed these results.[80] Unfortunately, mortality on the chemotherapy arm was 9%. This study also demonstrated a high salvage rate in the chemotherapy-naive patients treated initially with radiotherapy only.

Chan et al[78] reported a smaller study that did not demonstrate an advantage to using induction chemotherapy. In this trial, 82 patients were given either cisplatin and 5-FU infusion followed by radiotherapy, or radiation treatment alone. In this study, two courses of chemotherapy were administered, and the dose of the 5-FU infusion was only 60% of the standard dose. These factors may have affected the results of the study. The number of patients randomized was also small, and the median follow-up time was short—only 28 months.

In 1998, Chua et al[81] reported on the results of the Asian-Oceanian Clinical Oncology Association study comparing two to three cycles of cisplatin and epirubicin, followed by radiotherapy, vs radiation therapy alone. The two groups did not differ with respect to 3-year relapse-free and 3-year
overall survival rates. When only the evaluable patients (286/334) were analyzed, a trend toward an improved 3-year relapse-free survival rate was observed in the combined-modality group (58% vs 46%, \( P = .053 \)). In the subgroup of 49 patients with bulky neck nodes > 6 cm, a significant improvement in the 3-year relapse-free survival rate was noted in the combined group (63% vs 28%, \( P = .026 \)). A significant improvement in the 3-year overall survival rate favoring combination therapy (73% vs 37%, \( P = .057 \)) was also observed. However, as the follow-up of these patients was only 3 years, the results need to be confirmed over a longer period.

A randomized adjuvant chemotherapy trial was reported by Rossi et al.[70] In that study, 229 patients were randomized to radiotherapy alone, or radiation treatment followed by six courses of noncisplatin combination chemotherapy. No significant improvements in overall or relapse-free survival were observed. Our opinion, although based on nonrandomized trials, is that noncisplatin combinations are inferior to cisplatin combinations in nasopharyngeal carcinoma and cancers of other head and neck sites, and that this may have contributed to the negative results of this study.

A prospective, randomized, phase III intergroup trial, conducted in North America by the Southwest Oncology Group (SWOG) with the participation of the RTOG and Eastern Cooperative Oncology Group (ECOG),[82,83] obtained interesting results with concurrent cisplatin and radiotherapy. In this study, 193 patients were registered, and 185 patients were randomized and stratified to receive either radiation therapy alone (n = 92) to a total dose of 70 Gy, or a combination of chemotherapy and the same dose of radiotherapy (n = 93). The chemotherapy consisted of three cycles, every 3 weeks, of cisplatin at a dose of 100 mg/m² concurrent with radiation therapy, followed by three cycles, every 4 weeks, of cisplatin at a dose of 80 mg/m² on day 1 and 5-FU at 1,000 mg/m²/d (continuous infusion) on days 1 through 4. The adjuvant chemotherapy was given to enhance locoregional control and to decrease the incidence of systemic metastasis.

Patients were stratified according to T and N stage, performance status, and histopathology. All slides were reviewed centrally by an independent pathologist.

This important trial demonstrated a highly significant difference in overall survival rates at 3 years (46% for the radiotherapy group vs 76% for the chemotherapy/radiotherapy group; \( P < .001 \)), as well as a significant difference in progression-free survival rates (26% for the radiotherapy group vs 66% for the chemotherapy/radiotherapy group; \( P < .001 \)). Significantly fewer local, nodal, and distant metastases were observed in the combined treatment arm.

Possible reasons for the success of this trial include the facts that patients were stratified by important and accepted prognostic factors, and that total chemoradiotherapy was used in the investigational arm. Total chemoradiotherapy consisted of initial concurrent cisplatin and radiotherapy, used to achieve the best locoregional control; this was followed by adjuvant chemotherapy (three courses of cisplatin and 5-FU infusion), given to consolidate the response and to reduce the incidence of systemic metastasis.

This study clearly demonstrated that total chemoradiotherapy is highly effective in the treatment of locally advanced nasopharyngeal carcinoma. This approach is now considered the standard of care in the treatment of patients with locally advanced nasopharyngeal cancers.

In our recent experience with patients with locally advanced, previously untreated nasopharyngeal carcinoma, we administered induction chemotherapy consisting of 100 mg/m² of cisplatin intravenously on day 1, and 1,000 mg/m²/d of 5-FU via a continuous infusion on days 1 through 5, every 3 weeks, repeated for three courses. This was followed by standard radiotherapy and concurrent cisplatin, 80 mg/m² intravenously, every 4 weeks for three courses. The early results show that approximately 90% of patients with stage IV disease treated with this combined approach are alive more than 3 years later, and the majority of them are disease-free.

**Conclusions**

Chemotherapy is a very important part of the treatment of patients with nasopharyngeal carcinoma. Even in patients with recurrent or metastatic disease, chemotherapy, alone or with other palliative treatment, may be highly effective—conceivably achieving a 15% to 20% long-term survival rate. Cisplatin-based combination chemotherapy is most effective.

In patients with locally advanced, previously untreated stage III or IV nasopharyngeal carcinoma, combination chemotherapy given prior to, concomitant with, or following curative total radiotherapy improved local control, decreased systemic metastasis, and produced improvements in disease-free and overall survival in the majority of the studies reported. Concurrent chemoradiotherapy, followed by adjuvant chemotherapy, significantly improved local control, systemic control, progression-free
survival, and overall survival in prospective, randomized, phase III trials. Different sequences of
treatment modalities and newer chemotherapy agents need to be investigated in patients with
locally advanced nasopharyngeal carcinoma.

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