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

Drs. Ali and Al-Sarraf have prepared a comprehensive review of current data on the role of chemotherapy in the management of nasopharyngeal cancer, a tumor of epithelial origin with a distinctive geographic and ethnic distribution. Although this disease has traditionally been categorized as a head and neck neoplasm, its natural history and responsiveness to therapy differ considerably from those of other squamous cell carcinomas in the upper aerodigestive tract. Systemic chemotherapy has been accepted as the primary treatment for recurrent or metastatic nasopharyngeal cancer. For locally advanced, nondisseminated disease (which is amenable to curative therapy), there has been increasing interest in the addition of chemotherapy to radical radiation in an attempt to improve locoregional control and eradicate micrometastases.

Chemotherapy for Recurrent or Metastatic Disease

Patients with recurrent or metastatic nasopharyngeal cancer should be considered distinct from those with squamous cell cancers originating elsewhere in the head and neck. Chemotherapy is the mainstay of treatment for patients with recurrent or residual disease following radical radiotherapy, and after other salvage options including surgery and/or reirradiation have been explored. Chemotherapy is also offered as primary therapy to those who present with disseminated disease. Both groups of patients have outcomes superior to those reported for systemic treatment in their counterparts with other head and neck squamous cell carcinomas. Favorable physical characteristics such as young age, good performance status, and lack of comorbidities in nasopharyngeal cancer patients explain their better tolerability of the toxic side effects of chemotherapy.

Unique Biology

The biology of nasopharyngeal cancer is also unique among epidermoid cancers of the upper aerodigestive tract. Despite its propensity to metastasize to distant anatomic sites, nasopharyngeal cancer exhibits greater chemosensitivity and is associated with objective response rates to cisplatin (Platinol)-based combinations generally exceeding 50%, as indicated by Drs. Ali and Al-Sarraf in their review of the results of phase II investigations. In a recent review of 16 published reports,[1] Fandi et al identified 31 isolated cases of long-term survivors (3%) among 1,003 patients with metastatic nasopharyngeal cancer, thus supporting a curative role for chemotherapy in a small proportion of such patients. The Institut Gustave Roussy provided data on the largest published cohort of 20 long-term survivors who were treated for metastatic nasopharyngeal cancer in a single center over 18 years.[1] Long-term survivors were defined as patients who were disease-free for more than 36 months without treatment after attaining a complete response by chemotherapy. While the vast majority of long-term survivors have osseous metastases, prolonged survival is possible even with visceral involvement, for example, of the liver, lung, or lymph nodes.

New Agents

As pointed out correctly by Ali and Al-Sarraf, and echoed by other groups,[1,2] complete response to treatment is a prerequisite for long-term survival in recurrent or metastatic nasopharyngeal cancer, and untreated disease is uniformly fatal. Hence, there is a need to develop novel regimens that are capable of not only achieving but also maintaining durable disease remissions. Promising cytotoxic agents such as the taxanes and gemcitabine (Gemzar) are being evaluated alone and in combination with the platinum compounds. In addition, biological agents with activity against specific molecular targets such as inhibitors of the epidermal growth factor receptor (EGFR) and angiogenesis await assessment of their therapeutic benefit in this disease, when administered either concurrently with conventional chemotherapy or after significant cytoreduction postchemotherapy. Recent evidence suggests that latent membrane
protein 1 (LMP-1), an Epstein-Barr virus-encoded oncogenic protein, upregulates EGFR, thus rendering the latter an attractive antitumor target in nasopharyngeal cancer.[3]

**Combined-Modality Treatment for Primary Disease**

In their review, Ali and Al-Sarraf summarized data from nonrandomized and randomized trials in which chemotherapy was added to definitive radiotherapy in an attempt to improve the outcome of locally advanced nasopharyngeal cancer. It is important to recognize that nonrandomized trials help to estimate biological activity and establish feasibility, but because of the presence of selection bias, a comparison of patients in such trials with those from historical experience can lead to false claims of therapeutic superiority. This caveat was underemphasized by Ali and Al-Sarraf, and conclusions drawn from these comparisons must be interpreted with caution. Ali and Al-Sarraf outlined five prospective, randomized, phase III trials that evaluated the role of various types of adjunctive chemotherapy (neoadjuvant, concurrent, adjuvant, or combinations of these strategies) delivered in conjunction with radiotherapy in locally advanced nasopharyngeal cancer.[4-9] Details of these studies are summarized in Table 1.

**Neoadjuvant Chemotherapy**

Clinical trials of neoadjuvant or induction chemotherapy delivered prior to definitive therapy have yielded disappointing results in non-nasopharyngeal head and neck squamous cell cancers.[10] The potential limitations of neoadjuvant chemotherapy include stimulation of a repopulation of tumor cells during subsequent radiotherapy, selection of drug-resistant cells when the primary tumor (which may also be cross-resistant to radiation) is present, and enhancement of metastases when there are circulating tumor cells present.[11]

Three randomized trials of neoadjuvant chemotherapy have been conducted in locally advanced nasopharyngeal cancer, utilizing the BEC regimen (bleomycin [Blenoxane], epirubicin [Ellence], cisplatin),[4,5] cisplatin plus epirubicin,[6], and cisplatin plus continuous infusion of fluorouracil,[7] respectively. None of these trials demonstrated a survival advantage with neoadjuvant chemotherapy. In the VUMCA I trial, the high mortality rate (8%) in the BEC-plus-radiotherapy arm was attributed to the intrinsic drug toxicity occurring in patients with advanced disease, as well as the lack of a supportive care infrastructure in some institutions to manage complications in this multi-center study.[4,5]

In a preliminary report from the Asian-Oceanian group, neoadjuvant chemotherapy consisted of two to three cycles of cisplatin plus epirubicin administered prior to radiotherapy.[6] Based on an intent-to-treat analysis, no significant difference in relapse-free survival or overall survival was observed between the two treatment arms. The choice of induction regimen in this study might be regarded as suboptimal. In a subgroup analysis, patients with bulky neck nodes larger than 6 cm appeared to benefit from combined therapy, but this finding was based on a small number of patients and must be considered hypothesis-generating.

In the Hong Kong study by Chan et al, two cycles of cisplatin plus infusional fluorouracil were given prior to radiotherapy, and four cycles post-radiotherapy.[7] No significant difference in survival was observed, but the median follow-up duration reported in this small study was only 28.5 months.

**Adjuvant Chemotherapy**

The overview analysis of adjuvant chemotherapy trials in non-nasopharyngeal head and neck squamous cell cancers revealed no significant effect on survival of chemotherapy delivered after locoregional treatment.[10] In nasopharyngeal cancer, only one randomized study has examined the role of adjuvant chemotherapy administered after curative radiotherapy, and no survival benefit was observed from this intervention.[8] The chemotherapy regimen used in this study did not contain cisplatin, and compliance was poor—25 (22%) of 113 patients in the combined-therapy arm did not receive any or all of their drug treatments.

**Concurrent Chemoradiation and Adjuvant Chemotherapy**

The most promising results associated with the use of chemotherapy as an adjunct to definitive radiotherapy in nasopharyngeal cancer involve their concurrent delivery, and this benefit is also seen with chemotherapy administered concomitantly to radiotherapy in other head and neck cancers.[10] The Intergroup 0099 study is the first randomized study in nasopharyngeal cancer to demonstrate statistically significant differences in both progression-free and overall survival, favoring the addition of concurrent cisplatin during radiotherapy, followed by three subsequent cycles of adjuvant cisplatin and infusional fluorouracil.[9]

The results of this study should be interpreted cautiously for several reasons. First, while the acute toxicities were more severe in the chemoradiation arm, there is still no information available on the late toxicities of treatment. Second, a substantial proportion of the patients (24%) in this study had World Health Organization (WHO) grade I squamous cell carcinoma, which is not the most common
histology worldwide. The natural history of this histologic type and its response to treatment may differ from that of the more prevalent WHO grade II and III tumors. Therefore, results of this study may not be generalizable to populations where nasopharyngeal cancer is more endemic. In addition, only 9% of patients included in the Intergroup 0099 study had stage III disease according to 1992 American Joint Committee on Cancer (AJCC) criteria—a group that would now be classified as stage II by 1997 AJCC criteria.\[12\] Since it is based on such a small subset of patients with early disease, the conclusion that chemoradiation offers superior outcome in comparison to radiation for stage II tumors (1997 AJCC) warrants further confirmation.

Finally, the survival rates in the radiation-alone arm of the Intergroup 0099 study were inferior to those reported from other randomized trials in patient populations treated with single-modality radiotherapy. This trial was conducted in many centers, each treating a small number of patients, so that experience with the rather complex radiation plans required for this disease may have been limited in comparison to large centers that treat these patients frequently. Clinical load and experience are major determinants of outcome for several types of cancer.\[13\] so it is possible that in some patients in the Intergroup trial, chemotherapy compensated for suboptimal radiation. Despite these concerns, the results of the Intergroup trial are supported by evidence of benefit obtained from concurrent chemoradiation for other head and neck cancers as well as by results in other sites such as cervical cancer. In addition, the results of a phase III randomized trial from Hong Kong were reported recently at the Thirty-Sixth Annual Meeting of the Americal Society of Clinical Oncology.\[14\]

This trial, in which 99% of the 319 study patients had WHO grade II or III nasopharyngeal cancer, compared concurrent weekly cisplatin plus radiotherapy vs radiotherapy alone. With a median follow-up duration of 28.4 months, this study showed a trend toward improvement in 2-year progression-free survival using combined therapy, especially in patients with advanced Ho's T3 tumors (T3 and T4 by 1997 AJCC criteria), but no difference in overall survival.

**New Directions**

Continued follow-up is essential for both the Intergroup 0099 and the Hong Kong chemoradiation trials to provide definitive information on the effects of combined-modality treatment among different histologic subtypes, and on the long-term toxicity of such treatment. New and sophisticated radiation therapy techniques such as conformal radiation, brachytherapy, proton-beam radiation, and intensity-modulated radiation therapy, plus alterations in schedules such as accelerated and hyperfractionated radiotherapy, are actively being assessed for their utility in improving treatment outcome when delivered alone or in combination with chemotherapy.

While Ali and Al-Sarraf have identified the strengths of the current evidence on the role of chemotherapy in nasopharyngeal cancer, the maturation of results and long-term follow-up data from landmark studies will better define the treatment options in this disease. At the same time, continued efforts are ongoing to develop new anticancer agents and strategies that aim to further enhance the curability of this malignancy.

**References:**


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