Chemotherapy for Nasopharyngeal Carcinoma – Current Recommendation and Controversies

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KEYWORDS

• Nasopharyngeal carcinoma • Chemoradiotherapy • Therapeutic benefit
• Randomized trial • Meta-analysis

KEY POINTS

- Although chemotherapy has a major role in enhancing treatment outcomes, there is a wide variation in clinical practice and the best way to deliver chemotherapy is still clouded with controversies.
- Although timely and flexible modification of treatment strategy is necessary, whether it is time to move away from the established standard of care and what defines the highest level of evidence need to be asked.
- There are concerted efforts worldwide in promoting further advances in this important area and, with stronger global collaboration, it is hoped that future trials can address the current controversial issues.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) has a peculiarly skewed distribution; this is a rare cancer in North America but highly prevalent in Southeast Asia. The classical nonkeratinizing type is unanimously associated with Epstein-Barr virus (EBV). This cancer is notorious not only for its extensive local infiltration and early lymphatic spread but also its high propensity for hematogenous dissemination. A majority of patients present with advanced locoregional disease. It is important to understand the behavior and management of this unique cancer because it is highly treatable.

There is little controversy that radiotherapy (RT) is the mainstay of primary treatment. Locoregional control is steadily improving with advances in technology. A key problem to overcome is distant failure. For patients with locoregionally advanced disease, addition of chemotherapy serves dual purposes of potentiating RT for better locoregional control (especially for tumors infiltrating/abutting critical neurologic structures) and eradicating subclinical micrometastasis.

BACKGROUND FOR THE CURRENT GUIDELINES

Randomized phase III trials to evaluate the therapeutic benefit of various chemotherapy approaches have been initiated since 1979. It was not until 1998 that achievement of significant benefit in overall survival (OS) was first reported: this landmark was achieved by an Intergroup 0099 study (n = 193) using concurrent chemotherapy (cisplatin, 100 mg/m^2, every 3 weeks for 3 cycles) followed by adjuvant chemotherapy (cisplatin, 80 mg/m^2, and fluorouracil, 4000 mg/m^2, in 96 hours every 4 weeks for 3 cycles) during the post-RT period.[1,2] There was initial skepticism about the benefit of this regimen because the result of the RT-alone arm was substantially poorer than that achieved by major centers. Four confirmatory trials have subsequently been conducted[3–10]; although the magnitude of benefit was smaller, all concurred that concurrent-adjuvant chemotherapy could improve event-free survival compared with RT alone; all but one also reported significant improvement in OS.[11] This regimen has hence become one of the standard recommendations since the late 1990s.

The first patient-data Meta-Analysis of Chemotherapy in Nasopharyngeal Carcinoma (MAC-NPC), with 1753 patients from 8 trials, confirmed that addition of chemotherapy achieved a significant survival benefit compared with RT alone (absolute gain of 6% at 5 years).[12] Timing of chemotherapy was important. Only trials including a concurrent +/− adjuvant component achieved significant survival benefit; trials of adjuvant chemotherapy alone did not show significant benefit in any endpoint. This raised doubt about the exact magnitude of contribution by the adjuvant component in the Intergroup 0099 regimen. Furthermore, tolerance is often poor during the post-RT period, for only approximately 60% of patients can complete all 3 cycles of adjuvant chemotherapy after definitive concurrent cisplatin and radiation. It is desirable to eliminate adjuvant chemotherapy if its contribution above concurrent chemoradiation is minimal.

The concurrent regimen most commonly recommended is cisplatin, 40 mg/m^2 weekly, as used in the trial by Chan and colleagues[13] (n = 350). In the preliminary report, progression-free survival (PFS) was not significantly different between the concurrent arm and the RT-alone arm in the overall comparison (76% vs 69% at 2 years; P = .10), but PFS was significantly prolonged in the subgroup of patients with advanced T stage (P = .0075). In the subsequent report,[14] unadjusted analysis showed borderline significance in OS (70% vs 59%; P = .065); but the difference reached significance when adjusted for T stage, age, and overall stage (P = .049) for the whole series, particularly in the subgroup with advanced T stage (P = .013).