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EDITORIAL

Adjuvant Chemotherapy for Nasopharyngeal Carcinoma

To date, only two randomised studies on adjuvant chemotherapy in nasopharyngeal carcinoma (NPC) have been reported, with no survival advantage demonstrated in either trial.[1,2] However, drawing an analogy with breast cancer (Table),[3-37] one would expect that adjuvant chemotherapy is useful for the radical treatment of NPC, at least for patients at high risk of developing distant metastases, such as those with T3/T4 disease and/or advanced N-stage disease.[28-31]

Failure of the study by Rossi et al[1] to demonstrate the advantage of adjuvant chemotherapy could be due to the relatively low efficacy of the regimen used (vincristine, cyclophosphamide, and adriamycin rather than cisplatin-combination therapy), the high percentage of patients failing to receive the assigned treatment (13 of 113 patients randomised to the chemotherapy arm), and the lengthy interval (65 days) between completion of locoregional radiotherapy before commencement of adjuvant chemotherapy. Results of the Taiwan Cooperative Oncology Group (TCOG) study presented during the 2001 American Society of Clinical Oncology meeting differed from the preliminary findings reported in the published abstract.[2] In the update analysis, the study failed to show a reduction in distant metastasis or a survival benefit after adjuvant chemotherapy. This could be attributable to the high patient drop-out rate and the high non-cancer mortality rate seen in the chemotherapy arm. When patients were compared according to the actual treatments received, a trend towards less distant metastases after chemotherapy (p=0.07) was evident.

Both the Rossi et al[1] and TCOG[2] studies reported significant rates of patient non-compliance, in keeping with my own experience. In our randomised study comparing radiotherapy (RT) 'sandwiched' between neoadjuvant and adjuvant chemotherapy against RT alone, only 55% of patients completed the planned adjuvant chemotherapy due to poor tolerance.[38] Similarly, in the Intergroup 0099 study, only 55% of patients completed planned adjuvant chemotherapy.[39,40] The main limiting toxicity was oral and oropharyngeal mucositis with exacerbations during chemotherapy causing difficulties in feeding and swallowing. It thus appears that patients' tolerance for chemotherapy is poor following radical radiotherapy for NPC, which delivers a significant dose to the oral and oropharyngeal mucosa.

The efficacy of adjuvant chemotherapy is likely to be dose- and dose intensity-dependent. Therefore, delayed treatment courses and reduced chemotherapy doses may reduce the efficacy of adjuvant chemotherapy such that its value cannot be determined from small randomised studies. In a recent study using a 2 x 2 factorial design, patients (n=157) randomised to chemoradiation (Uracil + Tegafur + RT) treatment or RT alone were further randomly assigned to adjuvant chemotherapy after RT.[41] Here, patient compliance with adjuvant chemotherapy was again reduced, with 28.1% failing to complete all 6 courses. The lack of efficacy of adjuvant chemotherapy seen could again be attributed to inadequate chemotherapy treatment. The adjuvant chemotherapy regimen used (alternating cisplatin 100 mg/m^2 D1 and 5-fluorouracil [5 FU] 1000 mg/m^2 D1-3 [PF] and vincristine 2 mg, bleomycin 30 mg, and methotrexate 250 mg/m^2 [VBM] D1) could be criticised as suboptimal since the combination of 5 FU and VBM (VBMF) has been shown to be inefficacious for NPC.[42] Moreover, the power of the study was inadequate to show a small benefit in favour of adjuvant chemotherapy.

A Malaysian study has reported, however, that when adjuvant chemotherapy with cisplatin (100 mg/m^2 D1) and 5 FU (1000 mg/m^2 D1-D4) commenced soon after

Table. Comparison of response to chemotherapy: nasopharyngeal carcinoma (NPC) and breast cancer.

	NPC	Breast cancer
Response rate to neoadjuvant chemotherapy	82-98%[3-8]	50-90%[9-15]
Response rate of metastases to combination chemotherapy	45-79%[16-24]	41-90%[25-27]
Percentage of patients developing distant metastasis after radical locoregional treatment	27-33%[28-31]	15-55%[32-37] (T1abN0, T3N1)

radiotherapy (3-6 weeks) and was given in three courses three weeks apart, only 4/45 patients with Stage IV (non-disseminated) NPC (UICC 1987) developed distant metastases.[43] A 3-year actuarial overall survival rate of 80% after a median follow-up period of 52 months (range 11-118 months) was achieved. This survival rate is similar to that of patients in the chemoradiation arm of the Intergroup Study 0099.[39,40] Consequently, a randomised, multicentre study has started patient accrual in Malaysia. The study design compares chemoradiation treatment (as per the protocol used in the Intergroup study[39,40]) to RT followed by 3 courses of adjuvant chemotherapy (as per the protocol described by Prasad et al[43]). The study aims to differentiate the outcome associated with concurrent chemoradiation treatment from that of adjuvant chemotherapy.

At present, we should not dismiss the use of adjuvant chemotherapy in NPC. On the contrary, efforts should be directed towards improving the adjuvant approach through the use of more effective and less toxic drugs. A number of approaches appear worthy of testing in the adjuvant setting including:

- the use of chemo- and radiation-protectant agents such as amifostine;
- altered dose-scheduling (e.g. weekly cisplatin rather than 3-weekly cisplatin);
- continuous low dose 5 FU infusion throughout the entire treatment course rather than intermittent high dose 5 FU given over 4 to 5 days;
- oral tegafur and uracil as replacement for 5 FU; and
- the use of alternative active agents such as taxanes and gemcitabine.

Although the independent benefit of adjuvant chemotherapy has yet to be demonstrated, adjuvant chemotherapy with three courses of cisplatin and 5 FU remains an integral part of multimodality treatment for advanced nasopharyngeal carcinoma in the manner described by the Intergroup Study.[39,40]

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