Chemoradiation therapy in locally advanced nasopharyngeal cancer: which kind of cooperation?

Although radiation therapy is effective in the management of patients with early stage nasopharyngeal cancer, a high rate of local-regional failure and distant dissemination is expected in patients with advanced disease. This has prompted studies on the addition of chemotherapy to radiation therapy. Chemotherapy has been used as a neoadjuvant and, less frequently, concomitantly with radiation therapy or as an adjuvant to it. In this issue of *Annals of Oncology*, Oh et al. [1] report a small series of patients prospectively treated with neoadjuvant chemotherapy, followed by chemoradiation therapy (CCRT). This study is of interest because there are only a few other studies reported so far employing both neoadjuvant chemotherapy and CCRT [2, 3].

It is widely believed that the main benefit from CCRT should be local, by increasing the activity of radiation therapy, whereas the benefit from adjuvant or neoadjuvant chemotherapy should be systemic, by targeting micrometastatic disease. These are known, respectively, as the ‘local cooperation’ and the ‘spatial cooperation’ between chemotherapy and radiotherapy.

However, recent trials in nasopharyngeal cancer suggest an unexpected local cooperation for neoadjuvant chemotherapy, and, on the other side, concomitant chemoradiotherapy (CCRT) could result in a reduced metastatic rate, at least in some patient subgroups, thus displaying spatial cooperation.

Indeed, most of the evidence in favour of chemotherapy in nasopharyngeal cancer derives from studies using CCRT [4, 5]. A meta-analysis including >1,500 patients, randomized in six studies was published recently [6]. Most such studies employed neoadjuvant chemotherapy, while in one of them chemotherapy was included after radiotherapy, and in another chemotherapy was given concomitantly with radiation, followed by adjuvant chemotherapy. By combining these studies, a summary odds ratio of 0.62 (95% CI 0.52–0.78) was yielded, indicating a 37% increase in 2-year disease-free survival (DFS) and a 20% improvement in survival at 2 to 4 years in favour of chemotherapy. However, this survival benefit was substantially influenced by one study, the Intergroup trial [4], which used CCRT. Unfortunately, this trial included a large number of differentiated cancers (only 40% of cases had WHO type III nasopharyngeal cancer). This might in part explain the benefit from CCRT, in line with favourable results of CCRT in head and neck squamous cell carcinoma. An improvement in distant metastasis-free survival (DMFS) would have been expected mainly in undifferentiated nasopharyngeal cancer (UNPC), but the low number of these patients made it impossible to establish whether UNPC patients benefited from adjuvant chemotherapy. In addition, only 55% of patients received the planned three cycles of adjuvant chemotherapy, and 40% received one or no cycle. This challenges the feasibility of adjuvant chemotherapy in irradiated patients. That adjuvant chemotherapy is difficult in head and neck cancer patients has already been shown by previous studies. It follows that either cisplatin plus fluorouracil was so active in this series that these results were achieved irrespective of dose intensity, or most probably, CCRT yields its activity both at the local and the distant level, perhaps through better local-regional control [7].

After publication of the meta-analysis, four more randomized trials have been made available. All trials were carried out in geographical areas where the disease is endemic, so that a high proportion of UNPC patients were included [5, 8–10]. Three trials employed adjuvant or neoadjuvant chemotherapy, one only CCRT. The trial by Chi et al. [8] confirmed the negative results of an old trial [11], which showed that adjuvant chemotherapy, even if CDDP-based, is of no benefit (although with a lower systemic relapse rate). The study by Hareyama et al. [9] on neoadjuvant cisplatin and fluorouracil was able to show a favourable trend in DMFS, with no improvement in terms of DFS, survival or local-regional control. The trial by Chan et al. [10], mainly including CCRT patients, was unable to show a difference in terms of progression-free survival (PFS). However, PFS was significantly prolonged in patients with advanced tumour and nodal stage. The beneficial effect was obtained in this subgroup mainly by reducing distant failures, although a trend towards better local control was also observed. Finally, the most recent trial showed a significant impact from CCRT in terms of both DFS and overall survival. The main contribution of chemotherapy was seen at the tumour site, but also at the regional and distant sites, though without reaching statistical significance. By doing so, distant failures outnumbered local recurrences. Therefore, the results of Chan et al. [10] and Lin et al. [5] indicate a role for CCRT in improving local-regional control and DMFS. It is noteworthy that the only trial with a positive effect was that employing two cycles of concurrent polychemotherapy. These observations suggest that the maximal therapeutic benefit could be obtained by combining full-dose chemotherapy and CCRT. However, this can be done only when chemotherapy is given before CCRT. In fact, timing is critical, since the interaction between chemotherapy and radiation therapy may prohibitively increase the risk of side-effects, given the site of origin of this neoplasm. Generally, polychemotherapy is used when medical therapy is given in a neoadjuvant fashion, while single-agent chemotherapy is preferred when given in combination with radiation therapy. One might assume that polychemotherapy is more effective against systemic disease than monochemotherapy.
This is the background of treatment protocols such as that reported by Oh et al. in this issue [1]. These preliminary phase II studies suggest an excellent disease control and survival, with good tolerability and feasibility of both chemotherapy and radiation therapy, according to the planned schedules. In one trial, radiation therapy was delivered, mainly for tolerability concerns, at a total dose of 60 Gy, which may be considered relatively low. The achievement of excellent local-regional control in this series suggests that lower doses of radiation therapy may be acceptable if combined with chemotherapy. The reduction in tumour bulk at the T site would allow full irradiation of gross residual disease, thus maximizing local control and sparing normal tissues. This would imply lower late toxicity, which is still of some concern. Unfortunately, late toxicities from combined treatments in already closed studies have not been fully documented yet, and a more prolonged follow-up is needed.

Therefore, what next?

- Whether neoadjuvant chemotherapy followed by CCRT is superior to CCRT alone, or to CCRT followed by adjuvant chemotherapy, should now be tested within comparative trials.
- An effort should be made to identify patients who are most likely to benefit from neoadjuvant chemotherapy followed by CCRT. Who are they likely to be? Probably, those with both a high local and systemic risk, though one could not rule out that patients with just a high local risk might benefit, given the possible local cooperation of neoadjuvant chemotherapy with subsequent CCRT. A number of retrospective studies have attempted to identify patients who are more likely to fail at the primary site and/or distantly. Multivariate analyses showed that some factors may predict a higher risk of local failure and/or distant metastases [12, 13].

Regarding the first point, one should consider that new radiotherapy techniques, such as intensity modulated radiotherapy (IMRT), allowing both dose escalation and better treatment profiling, might challenge again the need for chemotherapy within integrated protocols. Secondly, incorporating an adjuvant chemotherapy arm in next-generation trials might be useless, for the very simple reason that adjuvant chemotherapy is hardly feasible, at least with the same dose/intensity as neoadjuvant chemotherapy.

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References
