

# Chemoradiation in head-and-neck cancer – are we any closer?

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A recent study analysed the timing of non-platinum chemotherapy in combination with radiotherapy in patients with head-and-neck cancer and showed that only those who had not undergone surgery benefited from the chemoradiation therapy. However, inconsistencies between some results of this study and those of previous studies, along with the advent of novel, less toxic combinations of radiotherapy, are likely to limit the development of the chemotherapy regimens used in their study.

In a recent study by Tobias and colleagues,<sup>1</sup> the authors report on the 10-year results of a UK head-and-neck trial (UKHAN1). This trial examined the effect of differential timing strategies of non-platinum chemotherapy administration, when combined with radiotherapy in patients with local advanced disease. In this study, 966 patients who had not undergone primary surgery were randomly assigned to receive either radical radiotherapy alone (group A,  $n=233$ ) or radiotherapy with two courses of chemotherapy (chemoradiation). Individuals receiving chemoradiation were given the chemotherapy on either days 1 and 14 of radiotherapy (group B,  $n=166$ ), days 14 and 28 after completing radiotherapy (group C,  $n=160$ ), or both (group D,  $n=154$ ). Patients who had previously undergone surgery were randomised to either radiotherapy alone ( $n=135$ ) or concomitant

chemoradiation alone ( $n=118$ ). In all cases, chemotherapy consisted of either methotrexate alone, or vincristine, bleomycin, methotrexate and 5-fluorouracil. The primary endpoints were overall survival and event-free survival.

Among patients who had not undergone surgery, only those assigned to group B benefited from the addition of cytotoxic agents to radiation therapy, regardless of the endpoint (median overall survival or event-free survival). However, in patients who had undergone surgery, chemoradiation did not yield any significant benefit compared with radiation alone. The authors also reported an increase in acute toxicity (and a subsequent reduction in patient compliance) with chemoradiation, especially for those in groups C and D, and in patients who had previously undergone surgery.

When interpreting the results of this trial, the first consideration relates to the

choice of drugs made by the investigators; a choice guided by the intention to use drugs less toxic and less expensive than platinum-derivatives. Did they achieve their objectives in terms of efficacy and drug safety profile? Upon reading these long-term results, one would be tempted to say these objectives were met “only partially”. Indeed, while the results of this study are consistent with those comparing chemoradiation to radiation alone in patients who do not undergo surgery,<sup>2</sup> they are in sharp contrast with data accumulated to date in a postoperative setting.<sup>3,4</sup>

The results of the study by Tobias et al.<sup>1</sup> are in contrast with those of the European Organisation for Research and Treatment of Cancer (EORTC)<sup>3</sup> and Radiation Therapy Oncology Group (RTOG)<sup>4</sup> trials, as they indicate that patients who have undergone surgery for head-and-neck cancer do not benefit from the addition of

cytotoxic agents to radiotherapy. There are several possible reasons for this discrepancy. First, EORTC and RTOG investigators used a platinum-derivative, identified by the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) meta-analyses<sup>2,5</sup> as the compound of choice for patients treated with chemoradiation. Second, non-compliance to chemoradiation in the UKHAN1 trial was significantly greater in patients treated postoperatively, compared with patients who did not undergo surgery (27% vs 8%).<sup>1</sup> Notwithstanding the intention of the authors to deliver drugs less toxic than platinum-derivatives, the result of this non-compliance is that treatment intensity was reduced in a significant number of patients who had previously undergone surgical intervention. Furthermore, the toxic effects reported were not fully unexpected if one considers the usual toxicity profile of drugs like bleomycin (pulmonary and gastro-intestinal toxicity, skin reactions) or methotrexate (gastro-intestinal toxicity, myelosuppression, skin reactions, liver function impairment). The poor patient compliance, together with the fact that the chemotherapeutic agents used are known to be less efficacious than platinum-derivatives, casts doubt on any additive or supra-additive effect of the regimens delivered in this study.

In the group of patients who had previously undergone surgery, the intention was to completely clear the tumour. This objective was not achieved in a significant number of patients because in both arms surgical margins were cleared in only 47% of cases. Moreover, the authors provide no information regarding the time intervals between surgical procedures and onset of radiation or chemoradiation, a parameter known to impact negatively on local control when it exceeds six to seven weeks.

Furthermore, the fact that the chemo-

therapy in this study, in some cases, consisted of methotrexate as the sole cytotoxic agent raises some concern. Indeed, in 1986 the South-East Cooperative Oncology Group (SECOG)<sup>6</sup> demonstrated that addition of 5-fluorouracil to the vincristine, bleomycin and methotrexate (VBM) regimen yielded better results than VBM alone. In addition, the methotrexate dose used by Tobias et al.<sup>1</sup> was 100 mg/m<sup>2</sup>, which is lower than the 200 mg/m<sup>2</sup> dose delivered in the SECOG study. In light of this, the chemotherapy schedule used by the authors might have been suboptimal.

The second consideration relates to patient compliance to treatment protocols. In patients who had not previously undergone surgery, only those in group B benefitted from the addition of chemotherapy to radiation. This finding actually mirrors the pattern of compliance to treatment protocols across the various treatment arms. There was considerable variation in compliance across the treatment arms, a factor that is likely to have significantly affected the reported efficacy because treatment intensity was significantly reduced, especially with respect to chemotherapy. This affect was particularly obvious in the arm that combined concomitant and maintenance chemotherapy in patients who had not undergone surgery, and in the treatment groups that combined radiotherapy and chemotherapy in a postoperative setting.

Interestingly, the direct relationship between poor compliance to chemoradiation and a less-favourable outcome is a systematic finding in this study. While a low level of non-compliance (8%) was associated with a significant benefit in patients treated by chemoradiation who had not undergone surgery, a high proportion of non-compliant patients in this study inevitably translated into an absence of therapeutic gain, regardless of the

sequence of treatment modalities. Specifically, non-compliance in patients who had not undergone surgery was 44% and 31% with regards to chemoradiation plus maintenance chemotherapy and maintenance (adjuvant) chemotherapy, respectively. The non-compliance rate was 27% for patients treated by chemoradiation who had undergone surgery.

In summary, the UKHAN1 trial attempted to identify a pragmatic alternative to platinum-based protocols for the treatment of head-and-neck cancer, with respect to treatment cost and toxicity. However, the volume of data generated throughout the past decade in favour of these latter protocols, as well as the advent of regimens based on the combination of less toxic, targeted therapies with radiation,<sup>7</sup> is likely to limit the impact of this study on the current use and future development of chemoradiation in head-and-neck cancer.

Details of the references cited in this article can be accessed at [www.cancerworld.org](http://www.cancerworld.org)

## Practice point

In contrast with recent data from randomised trials, which demonstrated a significant benefit in favour of the concomitant delivery of chemotherapy and radiotherapy for patients who undergo surgery, the present study did not elicit any benefit for non-platinum-based chemoradiation regimens in a postoperative setting. Beyond the fact that regimens using agents other than platinum-derivatives are known to be less efficient, this inconsistency might derive from the high rate of non-compliance to the treatment protocol observed in this trial, with a subsequent, significant reduction in dose intensities.