Concurrent cisplatin and radiotherapy versus cetuximab and radiotherapy, an unsolved problem

We read with great interest the paper by Ghi et al. [1], reporting the efficacy of induction chemotherapy (IC) followed by concomitant chemoradiotherapy (C-CRT) in patients with locally advanced head and neck squamous-cell carcinoma (LAHNSCC) in a phase II and III trial. The result of this study may potentially change our current practice for LAHNCC patients. However, we have some concerns about the study design, especially on the randomisation of the patients in C-CRT arms.

The data presented here are interesting and striking in different ways. First, previous studies demonstrated C-CRT is the standard of care, while IC has no effect on survival [2]. Second, cisplatin-based C-CRT is standard treatment in LAHNSCC and cetuximab is an alternative treatment option for the patients who cannot receive cisplatin [2, 3]. Magrini et al. [3] reported that patients treated with concurrent cetuximab and RT had less treatment compliance and also higher rates of acute toxicity compared with patients treated with concurrent cisplatin and RT. They reported that respective 1- and 2-year cause-specific survival rates were 75% and 68% in the cetuximab C-CRT arm 88% and 81% in the cisplatin C-CRT arm. Additionally, 1- and 2-year local control rates were 64% and 53% in the cetuximab C-CRT arm and 84% and 80% in the cisplatin C-CRT arm. Although there was not statistically significance in analysis and the study was closed early because of slow accrual, it is expected that patients treated with cetuximab C-CRT have inferior outcomes compared with cisplatin C-CRT.

Hence, investigating the standard and non-standard treatments in same study cohort may raise conflicting results with heterogeneous group of patients while randomizing the patients. In addition to that local progression-free survival for cisplatin C-CRT and cetuximab C-CRT is unknown in both C-CRT and IC followed by C-CRT arms. We believe that subgroup analysis of these patients might have a greater impact of papers intelligibility.

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Disclosure

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Reply to the letter to the editor 'Concurrent cisplatin and radiotherapy versus cetuximab and radiotherapy, an unsolved problem' by Guler et al.

We thank Guler et al. [1] for their interest in our recent publication [2] regarding the role of induction chemotherapy in locally advanced head and neck cancer.

In response to the concerns about the study design, especially on the concomitant arm, it should be noted that cetuximab/RT became a valid treatment option to concomitant chemoradiation within the time-frame of the study enrolment. Since this combination had become a treatment option, it would have been unfair to deny this option to patients, whilst on the other hand, the free choice of concomitant treatment by the investigators would have biased the results. For all these reasons, a single step double randomization was adopted (according to the reciprocal control study design) to prevent bias in the analysis of the time related events.

Since the results of the phase III trials comparing concomitant chemoradiation versus cetuximab/RT are not yet available, in our opinion the hypothesis of a different efficacy of the two concomitant strategies is only speculative. Up to now, only two randomized phase II trials comparing CCRT versus cetuximab/RT were published [3, 4]. The TREMPLIN trial [3] compared three cycles of concomitant high dose CDDP monotherapy versus CET/RT after three cycles of induction TPF in the contest of a larynx preservation program while the second trial [4] compared cetuximab with weekly cisplatin at 40 mg/mq. The latter trial [4] was clearly underpowered because it was closed early due to slow accrual after only 70 patients were enrolled. Moreover, treatment compliance (primary end point of the trial) was lower than expected in both arms since only 28% of patients received the planned doses of cetuximab and only 20% of patients received the seven planned cisplatin weekly administrations. Therefore, we do not agree with the statement of Guler et al. about a possible expected inferior outcomes for cetuximab/RT.