



# Adding to the debate on once-a-week versus once-every-3-weeks cisplatin dosing in concurrent chemoradiotherapy for locally advanced head and neck squamous cell cancer

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One of the most popular debates in locally advanced head and neck squamous cell carcinoma (LAHNSCC) is the optimal dose and schedule of cisplatin when combined with radical radiotherapy in the curative setting, both postoperatively and as definitive chemoradiotherapy (CRT). Hoping to settle this debate once and for all, we conducted a phase III randomized clinical trial to answer this question (1). We set out to evaluate if weekly cisplatin at 30 mg/m<sup>2</sup> was non-inferior to once-every-3-weeks cisplatin at 100 mg/m<sup>2</sup> as CRT in terms of locoregional control at 2 years. We found that it was not. In retrospect, it would be naive to expect a single trial to settle all questions related to this topic. Although our trial clearly proved that once-a-week cisplatin at 30 mg/m<sup>2</sup> is sub-optimal when used with concurrent CRT for LAHNSCC, the debate rages on regarding what dose and schedule of cisplatin is the winner. The reason for the controversy is that although the efficacy of once-every-3-weeks cisplatin at 100 mg/m<sup>2</sup> is unquestionable, the regimen is inconvenient and toxic. The head and neck oncology community has been searching for easier, less toxic regimens for decades.

Treatment de-intensification in order to lower toxicity has always been a dream in malignancies that are curatively treated and in which the patient is expected to have a good long-term survival. Some prominent examples include the move away from radical mastectomy to breast conservation therapy in localized breast cancer, and the use of adjuvant involved field radiotherapy as compared to extended field radiation following chemotherapy in patients with

early stage Hodgkin's lymphoma (2,3). In HPV-positive oropharyngeal cancer, Gillison and colleagues recently reported the results of their phase III randomized trial, in which cetuximab with radiotherapy was compared to the standard once-every-3-weeks cisplatin at 100 mg/m<sup>2</sup> with radiotherapy. They found that the patients treated with cetuximab with radiotherapy had a significantly shorter progression free and overall survival as compared to those treated with once-every-3-weeks cisplatin CRT (4). Thus, as attractive as the less intensive regimens may be and as logical and scientifically rational, we must exert extreme caution prior to adopting practices that are not the standard of care and have not been proven in well conducted adequately powered randomized trials. Our primary obligation is to not compromise patient outcomes.

When we offer CRT to patients who have undergone resection for LAHNSCC and have high risk features for recurrence, if we describe the benefits of CRT in terms of prolongation of locoregional control, progression free and overall survival, we are describing the benefits of the once-every-3-weeks cisplatin regimen. If we then treat the patient with any alternative cisplatin dose or schedule, the expectation of the outcome cannot be the same.

Since our trial, there have been several editorials and discussions in various forums. Some have suggested that perhaps a weekly cisplatin dose of 40 mg/m<sup>2</sup> may be an acceptable option. Let us examine the evidence that supports the use of cisplatin 40 mg/m<sup>2</sup> weekly as CRT for LAHNSCC. To the best of our knowledge, the evidence

for this regimen consists of retrospective case series and small phase II trials (5-7). Thus, there is an absence of direct comparative data proving the non-inferiority of weekly cisplatin 40 mg/m<sup>2</sup> to the once-every-3-weeks cisplatin at 100 mg/m<sup>2</sup> regimen as concurrent CRT for LAHNSCC. Several meta-analyses have compared the use of once-a-week to once-every-3-weeks cisplatin. A recent meta-analysis by Szturz *et al.* in 52 studies in over 4,000 patients, in both the definitive and adjuvant CRT settings reported no real survival difference between the two dosing regimens. The authors concluded that the evidence was insufficient and that prospective trials need to be performed that directly compare the once-a-week schedule to the once-every-3-weeks regimen (8). Similarly, with altered fractionation schedules as well, the meta-analysis suggested that the once-every-3-weeks cisplatin regimen should remain the preferred regimen (9). What is important to remember is that any meta-analysis can be only as good as the studies that have already been conducted and that constitute the meta-analysis. Since the strength of the evidence for the once-a-week cisplatin is weak, the conclusions of the meta-analyses will certainly be affected.

There are certain situations in which the once-a-week cisplatin dose regimen can be considered standard of care, for example in nasopharyngeal cancer (10). However, in other patients with LAHNSCC, once-every-3-weeks cisplatin should remain standard of care in radical CRT. Until we unequivocally prove that the once-a-week cisplatin regimen leads to similar efficacy as the once-every-3-week cisplatin regimen, we owe it to our patients to offer them the regimen that has been tried and tested and proven to be effective.

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