Commentary on “Weekly Low-Dose Versus Three-Weekly High-Dose Cisplatin for Concurrent Chemoradiation in Locoregionally Advanced Non-Nasopharyngeal Head and Neck Cancer: A Systematic Review and Meta-Analysis of Aggregate Data”

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“The Moving Finger writes; and, having writ,
Moves on: nor all thy Piety nor Wit
Shall lure it back to cancel half a Line,
Nor all thy Tears wash out a Word of it.”
—Omar Khayyám

Dr. Szturz and colleagues are to be congratulated on accomplishing a herculean task of comparing weekly versus three-weekly cisplatin treatment concurrent with radiation in both the definitive and postoperative setting for patients with squamous cell carcinoma of the head and neck. This retrospective analysis of 52 trials, which included over 4,000 patients, represents the largest data set in this space.

The take-home message for the readers should be that for the most important clinically meaningful outcome, overall survival, no differences could be demonstrated between weekly and three-weekly cisplatin in either the adjuvant or definitive chemoradiation settings. Rates of toxicity (AEs), endpoints that are much more difficult to compare outside of a randomized controlled clinical trial (RCT) setting, were more difficult to interpret. The data demonstrated far fewer grade 3 or greater acute AEs for the weekly cisplatin in the definitive setting (14 AEs favored weekly dosing, 2 favored three-weekly dosing). The scores were closer in the adjuvant setting. Four favored weekly dosing, two were equal, and eight favored three-weekly dosing. We should probably discount this math, for in addition to the problems with interpretation of these data outside of an RCT, how can we possibly equate one AE to another? Do anemia, thrombocytopenia, laryngeal toxicity, and constipation burden the patient to the same extent? This is an equation with no solution, or many solutions, depending upon whose math is being used.

My conclusions are different from the authors’. I do not agree that use of a weekly regimen should be labelled indiscriminate and premature. It is more reasonable to conclude, based upon the data presented here, that use of a weekly regimen is a very reasonable standard of care option. The position that weekly cisplatin should not be adopted as a standard until it is prospectively compared with the three-weekly high-dose schedule is not supported by the data presented. To the contrary, the fact that the investigators have failed to find a difference in overall survival is reassuring and validates what has become an acceptable alternative to high-dose three-weekly cisplatin dosing.

We are informed of Japanese, Portuguese, and Indian studies underway that prospectively address this question. However, these will not definitively answer the question either. The JCOG1008 trial plans to enroll only 260 patients. Noninferiority will be concluded if the upper limit of the confidence interval of the hazard ratio does not exceed 1.32. It would be shocking if there was a difference this large, and any difference within these limits will be judged to be nondefinitive because of the permissance of such wide margins. In other words, this study is underpowered to answer the question. The Tata Memorial Hospital has completed its randomized trial of 30 mg/m² cisplatin weekly (regarded by many as suboptimal dosing) versus 100 mg/m² every 21 days. Preliminary results from this trial presented at this year’s ASCO annual meeting failed to demonstrate a survival advantage of either dose regimen, and the curves are virtually superimposed.

The U.S. cooperative groups have already moved to adopt weekly cisplatin treatment concurrent with radiation in a number of their clinical trials. This is somewhat unusual for U.S. cooperative groups, whose habits are usually more conservative and based upon data from their own prior studies. This change was based upon an assessment by cooperative group members that weekly cisplatin seems to be as effective and less toxic than three-weekly cisplatin in the definitive setting. The data presented by Szturz et al. in this manuscript give us post hoc reassurance that the change to weekly cisplatin is acceptable.

Readers who routinely treat this patient population will not be surprised by no difference in overall survival yet improved compliance with intended therapy in the weekly schedule. Many of us who have been using the weekly regimen both as an acceptable standard of care and as part of clinical trials over the past several years have already experienced what the authors have demonstrated in this systematic review.
Taking a step back, a larger question is, should this question even be asked prospectively at this point? With limited resources for clinical trials, just how important is it to sort out the cisplatin dosing schedule in this disease? We already know that across many malignancies, including urothelial cancers, lung cancers, germ cell tumors, and ovarian cancers, the schedules of platinum used are highly variable. Unfortunately, even in 2017, the relevant pharmacology of platinum is poorly understood. It would take enormous trials to definitively sort out the optimal cisplatin regimen, with and without concurrent radiation, for each of these diseases.

We have more important work to do for our patients. We also lament the fact that while cetuximab has now been available for over a decade, we still have yet to sort out its role vis-à-vis cisplatin in any setting for head and neck cancers. The same can be said for our neglect of rigorous study of the taxanes with radiation. Unless we are willing to adopt a new paradigm of inexpensive, community-based studies with bare-bones data collection, our patients and our field would not be optimally served by going back to ask these questions. Their time has passed. It is not worth the resources required. We should be studying newer agents, which may prove to be more efficacious and less toxic, both in the concurrent chemoradiation setting and in the systemic treatment of recurrent and metastatic disease. It is appropriate and exciting to see trials underway that are designed to definitively ask whether immunotherapy combinations, for example, can be used instead of the omnipresent cisplatin-based recipes. The next generation of trials should focus on mutation-driven targeted therapies and immunotherapy. These trials should be prioritized over reshuffling chairs on the deck with respect to platinum dosing.

Are there other reasons for our inability to prospectively ask and answer questions such as dose and schedule optimization? Most trials are absurdly complex and driven not by the most important medical question but instead by regulatory approval priorities and inclusion of all constituencies of investigators. For example, many combined immunotherapy and chemoradiotherapy trial proposals for head and neck cancer patients with locoregional disease include experimental arms with extended adjuvant immunotherapy for as long as a year with no good scientific or clinical rationale. It is unclear who would benefit from such extended therapy, but such extended adjuvant treatment will devour precious resources. Academic clinical trialists aren’t off the hook either. We should be designing much more lean and efficient trials. The amount of data that we collect on each and every trial is unnecessary and contributes to our inability to move the field forward. Most trials require hundreds of data elements be collected, most of which are not relevant to the primary question being asked. We constrain dosing requirements to an extent not practicable once a treatment is adopted as standard of care. We restrict eligible patient populations to an extent that we cannot translate results into real-world patient settings. None of these restrictions are necessary for the conduct of important, clinically relevant trials.

So let’s move on. Let’s not call for prospective RCTs to answer every question. Let’s be highly selective about which questions are worth spending valuable resources to answer. Let’s prioritize those questions that are most important to patients rather than other constituencies. Let’s be ruthlessly efficient in our trial designs. Let’s disrupt the present paradigm, and abandon the fear that we are leaving a few crumbs undigested.

**Disclosures**
The author indicated no financial relationships.