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De-Escalation Strategies in HPV-Associated Oropharynx Cancer—Are we Putting the Cart Before the Horse?

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Background

Let's get to the punchline because it's a big one: **Radiotherapy plus cetuximab led to inferior overall survival in human papilloma virus (HPV)-positive oropharyngeal squamous cell carcinoma (SCC)**! It is in light of the recently published results from RTOG 1016 and De-ESCALaTE HPV that we scope this issue's Oncology scan to discuss the populist view that has prevailed among the head and neck cancer community for some time now – treatment de-intensification in HPV-positive OPSCC. Since the seminal analysis of RTOG 0129 by Ang and colleagues that HPV-positive OPSCC performs favorably relative to the majority of non-virally-driven head and neck cancers,¹ there has been substantial enthusiasm to design de-escalation treatment strategies with the primary intent of reducing radiotherapy-related toxicities. These have included reducing radiotherapy dose either outright (as currently being tested in the NRG-HN-002 randomized controlled phase II trial; [NCT02254278](#), [ClinicalTrials.gov](#)) or based on the tumor response to induction chemotherapy.^{2,3} Alternatively, several groups have also investigated switching the conventional “time-honored” concurrent cisplatin-radiotherapy regimen to perhaps a less toxic systemic agent. It was based on this rationale that the two complementary, landmark randomized controlled phase III trials were designed. The unexpected but pivotal results were published in *The Lancet* in January 2019.^{4,5} Both trials substituted 2-3 cycles of high

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dose cisplatin with cetuximab concurrent with radiation (70 Gy 35 fractions delivered in 6 weeks in RTOG 1016⁴ or 7 weeks in De-ESCALate HPV⁵). Both trials showed that the latter combination led to inferior survival, even at an early time-point of 2 years. Here, we will compare and contrast the trial designs, discuss key findings, and the implications of the results on clinical practice and ongoing/future research.

Study summaries

RTOG 1016

Maura Gillison, *et al.* describe the context in which RTOG 1016 was designed: cetuximab had recently been approved for the treatment of locally-advanced head and neck squamous cell carcinoma based on the level 1 evidence provided in 2006 by the “Bonner trial”.⁶ It was a drug that was described as less toxic than cisplatin and particularly effective for the oropharynx subsite. Clinical use of cetuximab increased substantially and the drug was often substituted for cisplatin in patients who were not medically suited for cisplatin or in patients who were thought to have low-risk disease. 5-year results of the Bonner trial were published in 2010 showing that cetuximab concurrent with radiotherapy reduced mortality by 27% over radiotherapy alone, corresponding to an absolute 5-year survival benefit of 9.2%.⁶ In that same year, Ang and colleagues published the seminal finding of RTOG 0129 in the *New England Journal of Medicine*, that HPV-status was a significant prognostic factor for overall survival in OPSCC.¹ Low-, intermediate-, and high-risk groups were defined based a stepwise approach: foremost by HPV-status, then smoking, and lastly, tumor and nodal categories. 3-year survival was an astounding 93% in the low-risk group compared to 46% in the high-risk group. The excellent prognosis of HPV-positive OPSCC patients and their young age at diagnosis led to the increasing concern of late toxicities associated with radiation and concurrent cisplatin, and the consequential impact on quality of life.

In this context, the RTOG designed a non-inferiority trial to compare overall survival for patients with HPV-positive OPSCC treated with radiotherapy plus cetuximab versus radiotherapy plus high dose cisplatin, hypothesizing that cetuximab would maintain overall survival while reducing acute and late toxicities. 182 centers in the US and Canada enrolled HPV+ OPSCC patients with American Joint Committee on Cancer (AJCC) 7th Edition T1-T2, N2a-N3 M0 or T3-T4, N0-N3 M0 disease, in what became one of the fastest accruing cooperative group trials ever. Randomization was 1:1, and patients were stratified by T category (T1-T2 vs T3-T4), N category (N0-N2a vs N2b-N3), Zubrod performance (0 vs 1) and tobacco smoking history (10 vs >10 pack-years). Cetuximab dosing was as per the Bonner trial; loading dose of 400mg/m² 5-7 days before initiation of RT, followed by 250mg/m² weekly for seven doses (total 2150mg/m²). Cisplatin was delivered on days 1 and 22 of radiotherapy (total 200mg/m²). All patients received accelerated intensity-modulated radiotherapy delivered at 70 Gy in 35 fractions over 6 weeks, with two fractions given on one day each week, at least 6 hours apart. HPV status was determined by p16 expression in a central laboratory, with “positive” defined as strong and diffuse nuclear and cytoplasmic staining of at least 70% of tumor cells. Quality of life outcomes were limited to the first 400 patients who consented and were assessed at baseline, end of treatment, and at 3 months, 6 months, and 12 months after treatment completion. Common Terminology Criteria for

Adverse Events (v.4) were used to collect acute (≤ 180 d) or late (>180 d) events relative to treatment completion.

Between June 9, 2011 and July 31, 2014, 987 patients were enrolled and 849 were randomized. 399 assigned to cetuximab and 406 assigned to cisplatin were subsequently eligible. Cetuximab and cisplatin were administered per protocol in 85% and 88% respectively and at least 95% of the planned 70 Gy dose was delivered to 95% of patients in both cetuximab and cisplatin groups. Radiotherapy plus cetuximab did not meet the criterion for non-inferiority, and overall survival (OS) was worse in the cetuximab arm (estimated 5-y OS 77.9%) versus the cisplatin arm (84.6%, $p = 0.0163$). This was driven by a worse progression-free survival (PFS) in the cetuximab arm (5-y PFS 67.3% vs 78.4% with cisplatin, $p = 0.0002$). The risk of locoregional failure with cetuximab was more than twice that in the cisplatin group (5-y recurrence rates 17.3% vs 9.9%), with no difference in distant metastasis. Interestingly, relative to treatment with cisplatin, patients with a Zubrod performance score of 1 did significantly worse with cetuximab (HR 2.66, one-sided 95% upper CI 4.32). After additional analysis, the authors could not determine why this was the case.

The proportion of acute grade 3-4 adverse events was similar between groups but the mean number of grade 3-4 acute adverse events per patient, or T-score, was significantly lower in the cetuximab group (raw T-score 2.35 vs 3.19, $p < 0.0001$), corresponding to a 40% lower acute toxicity burden. There were no significant differences in proportion of late toxicity events or feeding tube use between arms. EORTC QLQ-H&N35 scores were similar between arms at pretreatment, at end of treatment and at 1 year. Dental health was also scored similarly before and at 1 year after treatment.

The authors described several lessons learned for future trial design. First, high dose cisplatin remains the standard of care in platinum-eligible patients, including low-risk groups, decreased performance status and older age. Second, current promising phase II de-intensification strategies must be tested in non-inferiority trials with a control group of 70 Gy plus high dose cisplatin. Third, 5-year survival in RTOG 1016 (84.6%) was higher than radiotherapy plus cisplatin control groups of RTOG 0129 (3-y OS 82.4% for HPV+ OPSCC) and 0522 (3-y OS 85.6% for HPV+ OPSCC), emphasizing the importance of a contemporaneous control group.

De-ESCALaTE HPV

Hisham Mehanna, *et al.* designed their trial differently from RTOG 1016. Key differences included: 1) the primary endpoint, which aimed to demonstrate superiority in reduction of overall severe (G3-5) acute and late toxicities by 25% with cetuximab compared to the cisplatin combination; 2) a much smaller sample size compared RTOG 1016 (348 vs 987), as a result of the superiority study design; 3) a higher cumulative cisplatin dose intensity (300mg/m^2 vs 200mg/m^2) in the control arm, which was related to a difference in the radiotherapy fractionation schemes between the trials (non-accelerated in 7 weeks vs accelerated fractionated in 6 weeks for RTOG 1016). Nonetheless, these differences were likely inconsequential given the nearly identical primary conclusion from both trials.

Between Nov 12, 2012 and Oct 1, 2016, 348 patients were enrolled and 334 were randomized. 168 received cetuximab and 166 received cisplatin (162 and 159 were eligible for per protocol analysis, respectively). In the UK trial, 56 (17%) had T4, and 2 (1%) had N3 disease, which would be considered the highest risk group based on the latest AJCC 8th edition stage classification;^{7,8} this is comparable to the 1016 cohort (12% T4 and 4% N3), even though by the Ang criteria,¹ the former recruited only low-risk patients, while 29% of the latter cohort were intermediate-risk. An additional minor comment would be that HPV genotyping for 16, 18, and the other viral strains was performed using in situ hybridization (ISH) in the UK trial, which indicated discordance with p16-positivity in 6% of cases.

For their primary endpoint, this was a negative trial. There was no difference in severe toxicities (4.8%) between both arms; likewise no difference was observed when categorized into acute (4.4% [severe], 20% [overall]) and late events (mean 0.4 vs 0.5 [severe] and 9.4 vs 9.9 [overall] events per patient). This contrasts against the findings of reduced acute toxicity burden with cetuximab in 1016. Nonetheless, quality of life assessment using the same metric showed no difference at 1 year. Compounding this unexpected result, 2-year OS was worse with cetuximab than cisplatin (89.4% vs 97.5%, $p = 0.0012$). This was directly correlated with the significantly increased relapse rates, which like RTOG 1016, was primarily attributed to the higher local failures (2-y rates 16.1% vs 6.0%).

Commentary

Collectively, the outcomes of both trials caught the head and neck cancer community by surprise, notwithstanding the fact that both trials yielded such uncannily similar survival data. However, were the results truly unexpected or have we been consciously “ignorant” of the suggestive evidence? Contemporary data, including a meta-analysis⁹ suggests that cetuximab could result in equivalent survival to cisplatin, but more recent prospective evidence have perhaps already hinted that cetuximab may be a lesser partner with radiotherapy than cisplatin. RTOG 0522 failed to show any benefit when cetuximab was added to cisplatin-radiotherapy in locally advanced head and neck cancer patients; notably, OPSCC patients dominated the majority of patients in that study (70%; although p16-status was available for only a small subset of OPSCC patients).¹⁰ Consistent with other cancers, results showed that epidermal growth factor receptor (EGFR) expression did not predict for response to cetuximab. Even more concerning was the reported trend for worse PFS (HR 1.57; P for interaction = 0.12) and OS (HR 1.42; P for interaction = 0.13) in the subset of HPV-positive OPSCC cases. Separately, a small Italian randomized phase II trial comparing cetuximab- against cisplatin-radiotherapy also offered some early warning indicators.¹¹ While the study was not powered for survival, 2-year local control rate was only 53% with cetuximab, in contrast to 80% with cisplatin; admittedly, this might have been confounded by the fact that four patients in the cetuximab arm versus none in the cisplatin arm required an RT break of >10 days. Indeed, we have now learnt the harsh lesson of placing our faith in retrospective evidence, but to address the “elephant in the room” – what could have caused the increased local recurrence in this otherwise exquisitely radiosensitive tumor?

One possible reasoning would be that inferior radiotherapy plan quality contributed to the increased relapse rates in the cetuximab arm, since this is an established major determinant

of failure as shown in the TROG 02.02, HeadSTART study.¹² To this point, both RTOG 1016 and De-ESCALaTE HPV employed robust radiotherapy quality assurance processes, which would have addressed this potential confounder. We will have to await future reports to determine whether local progression occurred in the high dose field, at the margins, or in areas at risk treated to lower radiotherapy doses. Nonetheless, the results could simply be explained by the inferiority of cetuximab to cisplatin in targeting tumor repopulation after initiation of radiotherapy. Of note, HPV-positive and HPV-negative OPSCC are now known to be genetically distinct diseases; the former being enriched for mutations downstream of EGFR that may confer resistance to cetuximab.^{13,14} Another plausible but perhaps provocative theory is whether cetuximab “induces” a radioresistant phenotype in HPV-positive OPSCC tumor cells. Alluding to the radiotherapy dose deintensification trials, robust local control rates (2-y 93% and 100%) were achieved using 54-60 Gy in combination with concurrent paclitaxel after 2 cycles of induction paclitaxel and carboplatin (Chen *et al.*³) or concurrent cisplatin followed by limited neck dissection (Chera *et al.*¹⁵) in highly select patients, respectively. This lends itself to the opinion that cetuximab could potentially convert HPV-positive tumor clones from a radiosensitive to a radioresistant phenotype, which is not circumvented by dose escalation alone (to 70 Gy in RTOG 1016 and De-ESCALaTE HPV). Cetuximab has been shown to drive at least some of its effects through activation of innate immunity. Could cetuximab, when combined with radiotherapy, have altered the local tumor/immune microenvironment? These hypotheses need to be validated experimentally.

Interestingly, cetuximab was not less toxic than cisplatin when looking at proportions of acute and late toxicities, although the cumulative CTCAE symptom burden was greater with cisplatin. Patients, however, did not report cisplatin to be more impactful on their quality of life than cetuximab in both trials. The same observations were made in the combination trials with panitumumab – another anti-EGFR antibody, albeit this drug is purely humanized compared to cetuximab.^{16,17} This debunks the theory that substituting cetuximab for cisplatin results in reduced toxicities in patients who have poorer performance; in fact, skin and mucosa toxicities were increased with cetuximab or panitumumab! On the contrary, in doing so, we might be compromising on the outcome of the HPV-positive patient; in RTOG 1016, patients with poorer performance status (Zubrod 1) had the worst outcomes with cetuximab. This is especially important to note as we increasingly see an older patient cohort with this disease.¹⁸

The outcomes of these trials are a stark reminder that the excellent outcomes for HPV-positive OPSCC patients have been achieved with standard of care 70 Gy plus high dose cisplatin. What are the implications of these results on ongoing and future de-intensification trials? Given the promising data from the prospective phase II studies, we eagerly await the first results of NRG HN-002, which should inform us on the appropriate arm to take to a randomized phase III comparison against cisplatin and 70 Gy. We advocate for prudence and patience. It had been suggested that 70 Gy in an accelerated schedule might be sufficient to control the primary tumor, given the preclinical evidence that HPV oncoproteins contribute to increased radiosensitivity.¹⁹

What should we learn from these studies? First, these studies point to the importance of mechanistic-based science to guide implementation of novel therapies. To date, there remains no published data from preclinical systems suggesting that cetuximab-radiation provides equivalent radiosensitization to cisplatin-radiation. Second, our desire to “de-intensify” treatment for HPV-positive OPSCC should not blind us to the excellent outcomes we currently achieve with 70 Gy and cisplatin. Third, as a community, we should commit to ensuring that de-intensified treatments are tested in a randomized fashion against the standard of care prior to widespread adoption. Most importantly, we should acknowledge that biased hypotheses (“assumptions”) that are not systematically and robustly tested could result in detrimental outcomes. Long-term data from RTOG 1016 and De-ESCALaTE HPV will inform on the downstream consequences of these early local failures on the incidences of distant metastasis, even though there is no discernible difference from these early analyses. While it is laudable to decrease toxicity for patients with an excellent prognosis, these data are a timely reminder that our primary goal is “*first, do no harm*”.

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