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Abstract

Purpose. Among head and neck squamous cell carcinomas (HNSCCs), oropharyngeal cancer (OPC) was historically thought to be a homogenous entity, mainly caused by excessive alcohol and tobacco consumption. However, the discovery of human papillomavirus (HPV) infection as an independent risk factor for the development of OPC has led to changes in diagnostics and treatment of this cancer. HPV-positive OPC is associated with improved survival and reduced recurrence rates compared to similar stage HPV-negative OPC and HNSCC in general. These favorable outcomes have led the medical and scientific communities to consider de-escalation treatment options in this specific population to spare patients from unnecessary toxicity, without compromising survival. This comment aimed to critically evaluate de-intensification treatment strategies in HPV-related OPC and to propose future treatment approaches as well as trial design.

Methods. A review of the literature was performed.

Results. Among nine published non-surgical de-intensification trials, only three studies had a comparison head-to-head with the standard of care, with two trials demonstrating clear inferiority of de-escalating treatment option (cetuximab-based radiotherapy). Additionally, there has been significant heterogeneity among induction chemotherapy (IC) protocols in de-escalating studies. Also, the toxicity among these studies varies in terms of the manner of reporting (physician vs patient-reported adverse events).

Conclusions. Data obtained with de-intensified strategies should only serve to help select an appropriate experimental arm for a randomized controlled trial phase III comparison against cisplatin and 70 Gy of radiotherapy. Without a proper randomized trial, there remains the possibility of compromising survival, which raises ethical questions about conducting any de-escalation trial.

Short communication

The sixth most common cancer worldwide is head and neck squamous cell carcinoma (HNSCC). It is associated with high morbidity and mortality and represents a challenging subsite of cancer to treat [1].

Among HNSCCs, oropharyngeal cancer (OPC) was historically thought to be a homogenous entity, mainly caused by excessive alcohol and tobacco consumption. However, the discovery of human papillomavirus (HPV) infection as an independent risk factor for the development of OPC has led to changes in diagnostics and treatment of this cancer. HPV-positive OPC is associated with improved survival and reduced recurrence rates compared to similar stage HPV-negative OPC and HNSCC in general [2].

These favorable outcomes have led the medical and scientific communities to consider de-escalation treatment options in this specific population to spare patients from unnecessary toxicity, without compromising survival [3].

This comment aimed to critically evaluate de-intensification treatment strategies in HPV-related OPC and to propose future treatment approaches as well as trial design.

Numerous de-escalated therapy approaches have been introduced, including induction chemotherapy-based approaches, that select for appropriate de-intensification candidates versus, up-front reduced-dose chemotherapy, reduced-dose radiotherapy (RT), or both [4-10]. Also, there is interest in the replacement of traditional cytotoxic therapy with targeted therapy/immunotherapy as well as up-front surgery with or without adjuvant treatment based on histopathologic examination of tumor and neck dissection specimens.

One of the most promising strategies was considered to be the replacement of cisplatin (CDDP) with cetuximab (C225) therapy. This treatment approach was investigated in the two phase III randomized controlled trials (RCTs) (RTOG 1016, De-ESCALaTE), which both addressed the direct comparison of CDDP-based chemoradiotherapy and C225-based bioradiotherapy in virally induced OPC patients. The results revealed a pronounced superiority of the CDDP over C225 in terms of overall survival (OS) and disease recurrence [11,12]. Additionally, we have performed a meta-analysis which showed the superior efficacy of CDDP over C225 combined with definitive RT [13].

Given the consistent findings of both trials and the clear superiority of CDDP regarding the outcomes, the head and neck cancer medical community has been caught by surprise. Although, were the results so truly unexpected, or have we been ignorant regarding the evidence on platinum-based efficacy in trials from the past?

In a phase III RCT (IMCL-9815), C225 demonstrated a beneficial effect regarding OS and LRC given concurrently with RT in patients with locally advanced (LA) HNSCC compared to RT alone, without significantly detrimental effects regarding acute radiation toxicity [14]. The effect was most pronounced among OPC patients receiving altered fractionated RT. Based on these results, C225 was listed as a category 1 level of evidence in the NCCN guidelines as an agent to be given concurrently with RT in LA HNSCC for more than a decade. However, the efficacy of platinum-based compounds given concurrently with RT has been well-known. Before initiation of IMCL-9815 in 1999 we had evidence of platinum-based radiotherapy as a superior treatment compared to RT alone which was taken as the control arm in a "cetuximab registration study" [15]. This inappropriateness in the choice of the control arm has led to clinical practice for more than a decade, in which C225 was used as equivalent to CDDP in LA HNSCC. A consequence of this approach was increased financial toxicity together with the inferior treatment applied.

Mistakes have been made and will be made, but have we learned anything from them? It is hard not to notice that the inappropriateness of the control arm remains a chronic issue of this cancer setting. Among nine published de-intensification trials, the only study with head-to-head comparison (except RTOG 1016 and De-ESCALATE which demonstrated clear inferiority of cetuximab-based radiotherapy) with the standard of care was the Quarterback trial [9] which was terminated earlier due to financial concerns. Given the small numbers (n=20), the authors could not demonstrate the non-inferiority of the de-intensified arm against the standard arm in the form of cisplatin and 70 Gy of RT. **Table 1** shows published prospective series on non-sugical de-escalation in HPV-associated OPC [4-12]. Analyzing de-escalation trials, we noticed a significant heterogeneity of published series in numerous factors such as patient selection (included population) criteria as well as applied treatments, outcomes, and duration of trials/patient’s follow-up.

Therefore, several lessons should be learned from these de-escalation strategies.

Firstly, CDDP is a highly effective treatment given concurrently with RT for LA HNSCC regardless of HPV status and its efficacy has been proven through numerous phase 3 RCT trials

and thousands of patients. On the contrary, only one trial examined and demonstrated the efficacy of C225 in conjunction with RT in a randomized fashion [14]. Additionally, when tested head to head, CDDP was far more effective in terms of OS and LRR with a different profile of toxicity but surprisingly comparable rates of grade 3 or 4 toxicity [11,12].

Secondly, we believe that the data obtained with de-intensified strategies should only serve to help select an appropriate experimental arm for an RCT phase III comparison against cisplatin and 70 Gy of RT. All of the available de-escalating studies are single-arm prospective trials without a control arm in the form of a standard of care (CDDP-based RT). Thus, it's not possible to entirely exclude the chance that these patients received inferior treatment, which raises ethical issues regarding the conduction of such trials. Also, as a community of medical professionals, we should ensure that every intervention, including the de-intensified treatments, is tested in a randomized fashion against the standard of care before widespread adoption in routine clinical practice. Also, for ongoing phase 2 trials, interim analysis of end-points (such as PFS/LRR) two years after treatment is mandatory before proceeding to phase 3 RCTs. These curves between examined arms start to diverge earlier compared to OS which can help to prevent the further application of potentially inferior treatment of interventional arm.

Third, one of the crucial issues raised by the De-ESCALaTE and RTOG 1016 trials [11,12] is concern regarding the appropriate selection of low-risk patients for these trials. This issue unfortunately cannot be excluded using traditional risk factors such as TNM classification and smoking status. There is evidence that distinct genetic HPV-related subtypes exist which could potentially differ in chemo(radio)sensitivity as well as treatment response/outcomes. Therefore, we believe that identifying optimal HPV-associated de-escalation candidates should be driven by tumor genetic stratification in association with well-known clinical features.

Furthermore, there has been significant heterogeneity among induction chemotherapy (IC) protocols in de-escalating studies [4,8-10]. This heterogeneity is most profoundly pronounced by defining the cut-off response values that could enable the introduction of reduced-dose RT, as well as different agents, delivered concurrently with RT. Unfortunately, this kind of approach does not allow for making a clear conclusion on the most optimal backbone for IC and selection of ‘’best responders’’ who would be candidates for less intensified treatment. Also, the toxicity among these studies varies in terms of the manner of reporting (physician vs patient-reported adverse events).

Additionally, the financial toxicity of some of the de-escalation treatments seems to gain very little attention. We as clinicians need to also have a responsibility towards the costs of treatment, which have especially skyrocketed in the cancer setting over the last couple of years. Most importantly, we must embrace patient preferences as our treatment aims. In this specific case, the HNSCC patients strongly embrace survival as the most important endpoint, irrespective of the treatment costs, and increased toxicity [16]. Even is the context of toxicity concerns, CDDP-based radiotherapy provided more quality-adjusted life years (QALYs) and was less costly than C225-bioradiotherapy, strengthening its role as a standard of care for nonsurgical treatment of HPV-positive OPSCC [17].

Also, it should be emphasized that HPV-related OPC is a non-uniform group of tumors with diverse behavior across different risk groups. There is strong evidence on subsets of patients who are at high risk for distant failure, including those with T4 or N3 disease, involved lower neck involvement and five or more involved neck LNs [18-20]. In these patients, survival rates are poor and comparable to those with similar stage and non-virally induced HNSCC. Based on these findings there is an interest in regimens for escalating treatment assessing whether escalated radiotherapy, adding surgery, or immunotherapy will improve outcome and quality of life in these patients [21].

With a better understanding of HPV-associated OPC biological behavior and treatment approaches, the future will likely bring multiple de-escalated options as standard-of-care. Novel predictors of patients at risk for recurrence, such as hypoxia, circulating tumor DNA, and genomic dana, are likely to be important for additional risk stratification and choice of treatment within the next-generation trials. Additional factors that might impact outcomes could also be considered when designing future studies, including neutrophil/lymphocyte ratio, microbiome, body mass index, and nutritional markers.

In conclusion, without a proper randomized trial, there remains the possibility of compromising survival, which raises ethical questions about conducting any de-escalation trial. The hypothesis of less intensified treatment options for the HPV-positive OPC deserves additional scrutiny from the medical and scientific communities since it currently opens more questions than it provides answers to.

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Table 1. De-escalate prospective trials on HPV-associated OPC with published results.

Author, year	No of. patients[a]	RT dose and volume	Outcome/survival
Chen et al.[b] (2017)	44	cCR/cPR received 54 Gy/27 fx to areas of initial involvement and uninvolved cervical nodes received 43 Gy/27 fx; cSD and cPD received 60 Gy/30 fx or 48 Gy/30 fractions to the involved/uninvolved areas	2y PFS 92% 2y OS 98%
Chera et al.[c], (2018)	44	60 Gy/30 fx to high-risk regions, 54 Gy to subclinical areas; weekly CDDP, 30 mg/m2	3y CSS 100% 3y DMFS 100% 3y OS 95%
Chera et al.[c] (2019)	114	60 Gy/30 fx to high-risk regions, 54 Gy to subclinical areas at risk; weekly CDDP, 30 mg/m2 (n = 79); weekly C225 (n=10); no concurrent chemotherapy (n=25)	2y CSS 97% 2y DMFS 91% 2y PFS 86% 2y OS 95%
Gillison et al.[d] (2018)	406/399	70Gy/35 fx with CDDP (100 mg/m2 on days 1, 22 and 43 of RT) vs. 70Gy/35 with C225 (loading dose of 400 mg/m² one week before RT initiation + 250 mg/m² weekly for seven doses during RT)	5y OS 84.6/77.9%[e] 5y PFS 78.4%/67.3%[e]
Lee et al.[f] (2016)	33	60 Gy/30 fx for involved disease and 54 Gy/30 fx for subclinical disease; all received 10 Gy/5 fx boost to primary; if meeting imaging criteria, no boost given to node	2y DMFS 97%, 2y OS 100%
Marur et al.[b] (2017)	80/51	cCR received 54 Gy/27 fx to areas of initial involvement and uninvolved cervical nodes received 51.3 Gy/27 fx; non-cCR received 69.3 Gy/33 fx	2y PFS 80% 2y OS 94%
Mehanna et al.[d] (2018)	166/168	70Gy/35 fx with CDDP (100 mg/m2 on days 1, 22 and 43 of RT) vs. 70Gy/35 with C225 (loading dose of 400 mg/m² one week before RT initiation + 250 mg/m² weekly for seven doses during RT)	2y OS 97.5 /89.4%[e] 2y LRC 94/83.9%[e]
Misiukewicz et al.[b] (2019)	23/12	cPR/cCR randomized to 56 Gy/28 fx to involved areas and 50.4 Gy/28 fx to elective neck vs. 70 Gy/35 fx to involved areas and 56 Gy/35 fx to elective neck; cSD and cPD received the latter schema	2y, 3y PFS and OS 83%
Seiwert et al.[b] (2019)	62/50	Ang low-risk cases + >50% imaging response received 50 Gy/25 fx of RT to involved areas and next echelon nodes; low-risk cases + 30–50% response and high-risk cases + >50% response received 45 Gy/30 BID fx chemoRT and 30 Gy to next echelon nodes; others received 75 Gy/50 BID fx chemoRT and 45–54 Gy to next echelon nodes	2y PFS 95% 2y OS 98%

[a] second number indicates number of patients receiving de-escalated treatment

[b] induction chemotherapy studies (patients received sytemic therapy with CDDP, (nab)-paclitaxel or docetaxel before proceeding to response-dependent radiotherapy)

[c] reduced-dose chemoradiotherapy studies

[d] C225-based radiotherapy as de-escalated treatment option

[e] numbers related to C225-based radiotherapy

[f] node hypoxia-dependent radiotherapy trial