



## Two Sides of the Same Coin: Head and Neck Cancer Treatment De-Intensification and Intensification with Induction Chemotherapy

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The terms “intensification” and “de-intensification” are ubiquitous in the lexicon of head and neck oncology as the field moves toward individualizing treatment strategies on the basis of clinical factors such as TNM staging and biomarkers such as human papillomavirus (HPV). In this edition of *Oncology Scan*, we feature 3 articles linked by the theme of induction chemotherapy (IC), a treatment paradigm used for both intensification and de-intensification. The first 2 articles, by Marur et al (1) and Chen et al (2), study HPV-associated oropharyngeal cancer and examine the role of IC to select patients for radiation dose de-escalation. By intensifying systemic therapy and assessing the clinical response, the authors de-intensify the concurrent phase of therapy with the long-term goal of minimizing radiation-associated late effects.

The flip side of the coin is the use of IC to intensify treatment. A study from Italy by Ghi et al (3) has garnered discussion because it is a large trial ( $n = 414$ ), second only to the Spanish trial by Hitt et al (4) ( $n = 439$ ), and is the only randomized trial to show an overall survival (OS) and local–regional control benefit to adding IC to concurrent chemoradiation (CCRT). This result contrasts with prior trials that did not show a benefit to adding IC to CCRT, including the 2 US trials that were underpowered to meet the primary endpoint, DeCIDE (5) ( $n = 285$ ) and PARADIGM (6) ( $n = 145$ ). Although not practice-changing, the study by Ghi et al (3) does contribute to the continued discussion of which patients may benefit from treatment intensification with systemic therapy.

**Marur et al. E1308: Phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx-ECOG-ACRIN Cancer Research Group. *Journal of Clinical Oncology* 2017. (1)**

**Summary:** The Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN) 1308 study (1) was a single-arm phase 2 study of patients with stage III-IV HPV-associated oropharyngeal squamous cell carcinoma (OPSCC). Patients received 3 cycles of IC consisting of cisplatin, paclitaxel, and cetuximab. Patients who obtained a complete clinical response (cCR) at the primary site (as assessed by manual and endoscopic examination) received reduced-dose intensity modulated radiation therapy (IMRT) to 54 Gy (in 27 fractions) with concurrent cetuximab. Those with less than a cCR received 69.3 Gy radiation therapy (RT) (in 33 fractions). Involved nodes that achieved a cCR received 54 Gy, otherwise receiving 69.3 Gy. The primary endpoint was 2-year progression-free survival (PFS).

Ninety patients were enrolled at 16 ECOG-ACRIN sites from 2010 to 2011, with 80 patients evaluable and a median follow-up of 35.4 months. The majority of patients were stage T1-3 (89%), N0-N2b (69%), and non-current smokers (84%), with 49 patients (61%) having  $\leq 10$  pack-years of cigarette use. Fifty-six patients (70%) obtained a primary-site cCR to IC (with nodal cCR observed in 46 patients [58%]). Fifty-one patients went on to receive reduced-dose RT, with a 2-year PFS and OS of 80% and 94%,

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respectively. Subset analysis of tumor, nodal, and smoking status demonstrated a significant difference in 2-year PFS between those with <T4, <N2c and  $\leq 10$  pack-year smoking history (96%) versus those with T4, N2c, or >10 pack-year smoking (71%,  $P = .010$ ).

During IC, 57% of patients experienced grade 3 or 4 acute toxicity (mostly acneiform rash [28%], neutropenia [12%], and lymphopenia [6%]), with 3 patients unable to finish IC, 16 (21%) requiring dose reduction or cisplatin conversion to carboplatin, and dose modification of cetuximab during IC or RT in 22 (28%). Subset analysis was performed on 51 patients (42 receiving 54 Gy vs 9 receiving 69.3 Gy) completing the Vanderbilt Head and Neck Symptom Survey, version 2 at 12 months, showing that those who received  $\leq 54$  Gy had less difficulty swallowing solids (40% vs 89%;  $P = .011$ ) and lower rates of impaired nutrition (10% vs 44%;  $P = .025$ ).

**Chen et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: A single-arm, phase 2 study. *Lancet Oncology* 2017. (2)**

**Summary:** The University of California, Davis (Sacramento, CA) and the University of California, Los Angeles (Los Angeles, CA) performed a single-arm phase 2 study (2) of patients with stage III-IV HPV-associated (defined as p16 positivity on immunohistochemistry) OPSCC. Patients received 2 cycles of IC consisting of paclitaxel and carboplatin, followed by response-based IMRT with concurrent paclitaxel. Response to IC was assessed by computed tomography approximately 2 weeks after completion of IC, with complete and partial response defined, respectively, as 100% or  $\geq 30\%$  decrease in the sum of the longest diameters of target lesions. Patients with complete or partial response then received 54 Gy to primary tumor and involved nodes and 43 Gy to uninvolved nodal areas of the neck (over 27 fractions). Those with less than partial response received 60 Gy to primary tumor and involved nodes and 48 Gy to uninvolved neck regions (over 30 fractions). All RT was delivered via simultaneous integrated boost IMRT. The primary endpoint was 2-year PFS.

Forty-five patients were enrolled from 2012 to 2015, with 44 patients evaluable and a median follow-up of 30 months. Five patients (11%) had complete response at all sites, and 19 (43%) had partial responses. These 24 patients received lower-dose RT of 54 Gy, whereas the remaining 20 (45%) who had less than partial response received 60 Gy. Two-year PFS was 92%, and two-year locoregional control was 95%. Only 1 (2%) patient developed distant metastasis.

One patient was unable to complete IC and chemoradiation. During IC, 26 patients (39%) experienced grade 3 acute toxicity, which was mostly myelosuppression (no patients had grade 4 toxicity), and 3 (7%) required dose adjustments of chemotherapy during the second cycle of induction. One

patient (2%) was gastrostomy tube dependent at 3 months' follow-up, and no patients were dependent at 6 months.

**Comment:** Given the rise of HPV-associated OPSCC (7), with its outstanding disease outcomes (8, 9), many patients will experience long-term survival, but with the effects of chemoradiation. It is possible that many of these patients are being "over-treated" by current, standard treatment paradigms. Focused efforts on toxicity mitigation are therefore warranted.

Such efforts are currently underway, and these 2 trials (1, 2) represent one potential approach. Specifically, they use IC to select patients for whom dose-reduced RT may be safe and effective. The results of these 2 studies suggest that it may be as effective in select patients, given the reported 2-year PFS rates of 96% in patients with <T4, <N2c, and  $\leq 10$  pack-year history in ECOG-ACRIN 1308 (1) and 92% as reported by Chen et al (2). The question of whether using IC to reduce the intensity of CCRT results in less acute and late toxicity is less clear and not definitively answered by these phase 2 single-arm studies. They do, however, represent one approach (among many) to consider for subsequent phase 3 studies, and one possible future standard-of-care option.

Other approaches to "de-intensification" are subjects of current studies for this patient population. The Radiation Therapy Oncology Group 1016 (NCT01302834) phase 3 trial randomized patients between standard-dose (70 Gy) radiation with either 2 cycles of high-dose cisplatin or weekly cetuximab. NRG-HN002 (NCT02254278) is a randomized phase 2 trial of selected low-risk patients (T1-3, N1-N2b or T3N0,  $\leq 10$  pack-year smoking history) comparing 60 Gy accelerated RT with or without weekly cisplatin. In patients treated initially with transoral surgical resection and selective neck dissection, Eastern Cooperative Oncology Group 3311 is a phase 2 study using pathologic information to risk-stratify patients to postoperative observation for patients at low-risk of recurrence, adjuvant chemoradiation for patients at high-risk of recurrence, and randomization between lower-dose (50 Gy) versus standard-dose (60 Gy) adjuvant RT for intermediate-risk patients.

There are several questions and concerns about using IC as a means of selection that warrant mention. Are we trading one set of toxicities (RT-related) for another (chemotherapy-related)? The rates of grade  $\geq 3$  acute toxicities, including severe acneiform rash and myelosuppression, and subsequent chemotherapy dose modifications during IC observed in both studies show that treatment with IC requires careful patient management. This also does not even take into account the additional cost and time added by inserting a regimen of chemotherapy before the initiation of the definitive treatment modality (RT). Do we even need IC to allow for RT de-escalation? If NRG-HN002 demonstrates that 60 Gy (with or without chemotherapy) is sufficient, then IC may be rendered moot.

These trials help establish the foundation for future, standard patient treatment for HPV-associated OPSCC.

Until the results of current or pending trials mature and are reported, we would currently still advocate for standard treatment approaches in the off-study setting. However, the era of “personalized,” “precision” medicine is coming. It is likely that there will not be one “standard” approach to toxicity mitigation, but with improved up-front diagnostics and stratification, one could envision a true risk-stratified approach in which the answers may significantly differ between groups of patients. For patients who have minimal risk of either locoregional or distant failure, perhaps surgery alone or reduced-dose radiation monotherapy will be the solution. For those at high risk of locoregional failure, standard-dose chemoradiation or even trials of novel radiosensitizers may be the answer. Patients for whom the risk of disease recurrence is systemic but not locoregional may be an ideal population for trials examining novel tumor vaccines or immunotherapy in the adjuvant setting. Alternatively, it may be in this setting that IC has a role in improving survival by reducing distant metastases (similar to the observation in Epstein-Barr virus–associated nasopharynx cancer) (10). There is still much work to be done to give patients their most individually effective yet least toxic therapy. These 2 articles represent an initial first step at the beginning of this journey.

**Ghi et al. Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced head and neck cancer. A phase II-III trial. *Annals of Oncology* 2017. (3)**

**Summary:** This multicenter, open-label, randomized phase 2-3 trial randomized patients with locally advanced head and neck cancer to IC followed by CCRT or CCRT alone. The trial accrued 421 patients from 48 centers in Italy from 2003 to 2012 and began as a phase 2 study that randomized patients to 3 cycles of induction docetaxel, cisplatin, and 5-fluorouracil (TPF) every 3 weeks followed by concurrent cisplatin-fluorouracil (PF)-CCRT (cisplatin 20 mg/m<sup>2</sup> day 1-4 plus 5-fluorouracil 800 mg/m<sup>2</sup>/d, 96-hour continuous infusion) versus the PF-CCRT regimen alone. The phase 3 extension of the trial included a 2 × 2 randomization such that patients received either concurrent PF or concurrent cetuximab. The final arms were therefore (1) IC followed by PF-CCRT, (2) IC followed by cetuximab-CCRT, (3) PF-CCRT, or (4) cetuximab-CCRT. The population consisted of patients with stage III-IV locally advanced head and neck squamous cell carcinoma (LAHNSCC) of the oropharynx (56%), hypopharynx (23%), and oral cavity (20%) who were technically unresectable, medically inoperable, or were deemed to have low surgical curability (T3-4, N2-3 excluding T1N2). Patients were stratified by T stage, N stage, and primary site; HPV was not assessed. Radiation was standard fractionation to 70 Gy using 3-dimensional conformal RT or IMRT. The study was powered to assess an OS difference between IC versus

CCRT and not to evaluate differences in oncologic outcome based on concurrent treatment strategy.

With a median follow-up of 44.8 months, the IC arms had significantly improved median OS of 54.7 versus 31.7 months for CCRT arms (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.56-0.97; *P* = .031) and a lower local–regional failure rate of 41% versus 48% for CCRT arms (HR 0.74; 95% CI 0.55-0.98; *P* = .036). There was no statistically significant difference in distant failure with or without local–regional recurrence (HR 0.76; 95% CI 0.46-1.25; *P* = .274). Most patients in the IC arms received all 3 cycles of TPF (194 of approximately 204 patients). There were similar rates of concurrent chemotherapy dose modification, RT completion (93% in both arms), and RT interruption of >3 consecutive days (30% in CCRT arms and 27% in IC arms). On subgroup analyses, the OS benefit was isolated to the non-oropharynx sites (IC vs CCRT, HR 0.66; 95% CI 0.44-0.99) and not significant for the oropharynx subsite (IC vs CCRT, HR 0.83; 95% CI 0.56-1.22). When analyzed according to concomitant treatment type, the OS benefit was confined to patients who received concurrent cetuximab (IC vs CCRT, HR 0.57; 95% CI 0.35-0.92) and not statistically significant in the PF-CCRT arms (IC vs CCRT, HR 0.83; 95% CI 0.58-1.19).

**Comments:** Although this Italian study is the first randomized controlled trial to demonstrate an OS and local–regional control benefit with the addition of IC to CCRT, the findings are not broadly applicable to all LAHNSCC patients. Rather the study raises questions as to which patients may benefit from such an approach. Three prior randomized trials did not show an OS advantage of adding IC to CCRT. These include the largest study from the Spanish H&N Cancer Cooperative Group trial (4) and the 2 US studies, DeCIDE (11) and PARADIGM (6), both of which were underpowered owing to low event rates in the HPV era. Although these trials all aimed to identify a benefit of adding IC to CCRT, they differed in their patient populations, trial designs, and both the induction and concurrent chemotherapy regimens. The patient population for the Italian study by Ghi et al (3) is likely to have a lower rate of HPV-related oropharyngeal cancer than the US trials (6, 11) and represents a population with a higher risk of treatment failure. The OS in the Italian study (3) is closer to that of the Spanish trial (4), which had a median OS of only 27.6 months for CCRT; yet the Spanish trial showed no benefit to adding IC to CCRT (4).

Even though a potential reduction in distant metastases is a rationale for using IC, this study (3), as in the other randomized trials (4, 6, 11), did not demonstrate a statistically significant reduction in distant metastases with the use of IC. The reduction in local–regional failure seen in the IC arm has not been demonstrated previously. It is possible that this is related to the concurrent chemotherapy regimens. Given that at least one small randomized trial that terminated early suggested inferiority of cetuximab to

weekly cisplatin (12), it is possible that adding IC improved outcomes for a potentially inferior concurrent regimen (the cetuximab-CCRT arms). Although underpowered, the subgroup analysis does suggest that the IC benefit in this study was only seen among patients receiving concurrent cetuximab. Additionally, the cumulative cisplatin dose in this study is 160 mg/m<sup>2</sup>, lower than the 200-300 mg/m<sup>2</sup> dose target utilized for CCRT. Yet in this study the patients received infusional 5-fluorouracil in addition to cisplatin. In fact, each trial comparing IC plus CCRT versus CCRT has different concurrent regimens: the Spanish trial used 3 cycles of bolus cisplatin, the DeCIDE trial used the “DHFx regimen” (docetaxel, fluorouracil hydroxyurea with concurrent twice-daily radiation), and PARADIGM used concurrent carboplatin or docetaxel after IC and 2 cycles of bolus cisplatin in the CCRT-alone arm.

The authors themselves conclude by stating that IC cannot be considered the standard of care for LAHNSCC but that IC before CCRT may improve outcomes for select patients. The question remains as to who these patients are. This approach may be particularly relevant for unresectable non-oropharynx patients with a good performance status, who are likely to tolerate IC without compromise of the CCRT phase of treatment. The individual patient data meta-analysis of chemotherapy in head and neck cancer (MACH-NC) (13) showed that the greatest benefit of chemotherapy was seen when given concurrently with RT. One clear limitation to the meta-analysis was that the optimal induction regimen of TPF was not included in the analysis because the TAX 323 (14) and TAX 324 (15) studies had not yet been completed. On tumor site-specific analysis (16), the MACH-NC confirmed that the benefit of chemotherapy was greatest when given concurrently for all tumor sites. Yet there was no significant interaction between chemotherapy timing and survival in oral cavity and hypopharynx tumors, suggesting that alternatives to concurrent CCRT alone may yet yield benefit. Whether IC is the optimal intensification strategy also depends on the anticipated ability of the patient to tolerate toxicities of IC, such as myelosuppression (27.5% patients in Ghi et al [3] developed grade 3-4 neutropenia).

Although the study by Ghi et al (3) is not practice-changing, it raises questions regarding the importance of patient selection and optimal chemotherapy for the induction and concurrent phase of radiation therapy. The role of IC continues to be explored for organ preservation, improving oncologic outcomes for select patients, and response-adapted therapy whereby patients are selected for subsequent therapy according to induction response.

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