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Head and Neck Cancer (CP Rodriguez, Section Editor)

Therapeutic Intensification and Induction Chemotherapy for High-Risk Locally Advanced Squamous Cell Carcinoma

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Opinion statement

The treatment of HNSCC has rapidly evolved over the past 30 years and multidisciplinary management is required, especially for locally advanced disease (LAHNSCC). Concomitant chemoradiation (cCRT) is the standard of care and cetuximab/RT (CET/RT) is an alternative treatment option, especially for patients unfit for concurrent cisplatin. Several intensification strategies have been explored to improve the outcome of the concomitant treatment. The combination of cisplatin plus cetuximab concurrent to RT failed to improve overall survival (OS) in two phase III trials. Induction chemotherapy (IC) has a proven role in organ preservation; however, its ability in prolonging OS has not been clearly demonstrated. Immune checkpoint inhibitors (ICIs), specifically anti PD-1 inhibitors, have been recently approved for the treatment of patients with recurrent/metastatic platinum-refractory disease. Recent clinical trials are exploring the role of immunotherapy at earlier stages of the disease in combination with concomitant treatments. The purpose of this article is to review current evidence regarding treatment intensification strategies for LAHNSCC (except nasopharyngeal carcinomas) with particular emphasis on the role of induction chemotherapy.

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) represents 5% of newly diagnosed cancers in adults and more than 550,000 new cases are predicted annually worldwide [1].

Most HNSCC are related to tobacco and alcohol; however, since 2005, high-risk human papilloma virus (HPV) infection has also been recognized as a risk factor for some oropharynx cancers involving tonsils and base of tongue. Despite the better prognosis of HPV-related oropharynx cancers, no evidence for different treatments (i.e., treatment de-intensification) is available so far.

The treatment of HNSCC has rapidly evolved over the past 30 years and multidisciplinary management is required, especially for locally advanced disease (LAHNSCC). Concomitant chemoradiation (cCRT) is the standard of care with the best supporting evidence [2], and cetuximab/RT (CET/RT) is an alternative treatment option [3, 4].

Immune checkpoint inhibitors (ICIs), specifically anti PD-1 inhibitors, have been recently approved for the treatment of patients with platinum-refractory recurrent/metastatic disease. Several clinical trials are now exploring the role of immunotherapy at earlier stages in combination with concomitant treatments (concurrently or sequentially) or as pre-operative treatment in resectable patients.

The purpose of this article is to review current evidence regarding treatment intensification strategies for LAHNSCC of the oral cavity, /oropharynx, /hypopharynx, and larynx (nasopharynx excluded) with particular emphasis on the role of induction chemotherapy (IC).

Standard treatment of LAHNSCC

Most patients with HNSCC present loco-regionally advanced disease not suitable for radical resection or with low surgical curability.

Several phase III trials and the individual patient data meta-analysis of chemotherapy in head and neck cancer (MACH-NC) [2, 5] have shown that cCRT allowed statistically significant overall survival (OS) improvement vs RT alone (absolute benefit 6.5% at 5 years, HR 0.81, 95%CI 0.78–0.86; $p < 0.0001$) [2, 5]. Platinum-based regimens have shown to be more effective than others (HR 0.75 vs 0.86; $p < 0.01$). However, no specific analysis regarding the effect of different platinum compounds (cisplatin or carboplatin), of the cisplatin total dose and number of cycles has been performed. The only information available regarding the importance of the concomitant cisplatin total dose comes from an old ECOG trial [6] in which a low-dose of cisplatin (20 mg/mq) was administered weekly during RT for a total dose of 140 mg/mq. Since no survival advantage vs RT alone was reported, 140 mg/mq total dose is considered ineffective for concurrent cisplatin monotherapy.

In 2006, a phase III trial showed that cetuximab concomitant to RT also provides significantly superior OS and loco-regional control (LRC) vs RT alone [3, 4]. Up to now, CET/RT has been considered an alternative treatment option to cCRT [2, 3], especially for patients unsuitable for concomitant cisplatin, pending the results of the phase III trials comparing the two concomitant strategies.

The National Comprehensive Cancer Network (NCCN) guidelines [7] recognized three concurrent systemic therapies as "category 1": cisplatin high dose (100 mg/mq for three cycles), three cycles of carboplatin + 5-fluorouracil (5FU), and weekly cetuximab. Literature data has reported suboptimal compliance to three cycles of concomitant chemotherapy (both for cisplatin high dose and for

carboplatin + 5FU) and about 30% of patients are unable to receive the three planned cycles [8, 9]. Subset analyses seem to suggest that two cycles of concomitant cisplatin monotherapy (200 mg/mq total dose) may be as effective as three [8] but no randomized trials have been conducted to confirm this hypothesis.

Treatment intensification strategies

In the last few years, several intensification strategies have been explored to improve the outcome of the concomitant treatment. The combination of cisplatin plus cetuximab concurrent to RT and IC followed by concomitant treatment (i.e., sequential strategy) has been investigated in phase III trials.

Concurrent cisplatin plus cetuximab

Despite the adverse events reported in the first single-arm trial published in 2006 [10], preliminary encouraging survival data (76% OS at 3 years) supported subsequent studies to better assess the role of this intensification strategy.

Two phase III trials [11, 12•] comparing the triple combination (cCRT + cetuximab) have been completed. In the RTOG-0522 [11] trial, the control arm was cCRT [two cycles of high-dose cisplatin concurrent to accelerated concomitant boost RT (AFX-C)] while in the GORTEC 2007.01 trial [12•], the reference arm was CET/RT. Both trials failed to demonstrate OS advantage, and they also showed a poor toxicity profile for the experimental arms. However, the GORTEC trial [12•] met the primary endpoint of progression-free survival (PFS) with an HR of 0.73 (95%CI 0.57–0.94; $p = 0.015$). A significant advantage was also reported for LRC: HR 0.54, 95%CI 0.38–0.76; $p = 0.00$. It should be noted that the GORTEC 2007.01 trial randomized patients with limited nodal spread (N0-N2a, N2b allowed if non-palpable) and that concurrent chemotherapy consisted of three cycles of carboplatin + 5FU during standard fractionated RT (St-RT). Due to the benefit observed in LRC and PFS, this intensive treatment could be an option for selected patients unsuitable for cisplatin-based chemoradiation. However, it could have a limited clinical impact also because of the poor toxicity profile.

Rationale for induction chemotherapy outside the organ preservation programs

Although IC has a proven role in organ preservation and in reducing distant metastases [2, 5], its ability to prolong OS has not been clearly demonstrated.

The rationale for IC is quite strong. Previously untreated head and neck squamous cell carcinomas are chemosensitive tumors and high responses (70–80%) have been reported since the early 90s with the cisplatin + 5FU (PF) combination [13, 14]. As a consequence of tumor shrinkage, an improvement both in cancer-related symptoms and in quality of life (QoL) is usually reported. Moreover, response to IC is predictive of different outcomes to the subsequent nonsurgical treatment, with a good response leading to better LRC by (chemo)radiotherapy [15]. For these reasons, response to IC is the criteria historically used to select patients candidate for organ preservation.

The MACH-NC meta-analysis [2, 5] also evaluated the effect of IC. A HR of death of 0.96 (95%CI 0.90–1.02, $p = 0.18$) was reported for IC followed by loco-regional treatment vs loco-regional treatment alone. The corresponding small absolute OS benefit (2.4% at 5 years) was neither statistically significant nor clinically relevant. Conversely, a significant advantage for IC was reported in distant control (HR 0.73, 95%CI 0.61–0.88, $p = 0.001$). When the analysis was limited to induction PF, a statistically significant advantage was observed both in OS (HR 0.90; 95%CI 0.82–0.99, about 5% absolute advantage at 5 years) and in distant control (HR 0.63; 95%CI 0.45–0.89).

Since the early 2000s, more effective IC regimens have become available. Most of the phase III trials comparing induction PF vs PF plus a taxane (TAX-PF) [16–19]—usually docetaxel—showed an increase in CRs, PFS, and OS for the three-drug combination. The most recent MACH-NC meta-analysis [20] focused on induction PF vs Tax-PF, demonstrated a statistically significant benefit for the Tax-PF combination in PFS (HR 0.78; 95%CI 0.69–0.87; $p = 0.001$), OS (HR 0.79; 95%CI 0.70–0.89; $p = 0.001$), and distant control (HR 0.63, 95%CI 0.45–0.89; $p = 0.009$). Interestingly, a significant reduction in loco-regional failure (HR 0.79, 95%CI 0.66–0.94; $p = 0.007$) was observed for Tax-PF, and this was the first demonstration that IC could positively affect LRC. Except for leukopenia, neutropenia, and febrile neutropenia, the toxicity profile was more favorable with Tax-PF and an improvement in the QoL was reported in the trial exploring this issue [16].

Because of these data, docetaxel/cisplatin/5-fluoroutacil (TPF) has now been established as the standard IC regimen.

IC followed by concomitant treatment (i.e., sequential strategy)

Five phase III trials [21–23, 24•, 25] have explored the role of induction TPF before concomitant treatment vs concomitant treatment alone (Table 1). The trials were not homogeneous because of different study designs, different patient populations, different concomitant treatments, different TPF doses, and number of cycles (two or three). Moreover, they led to different conclusions.

The first published was the PARADIGM trial [21]. Patients with stages III–IV (resectable or unresectable) were randomized to receive three cycles of high-dose cisplatin concomitant to AFX-C vs three cycles of induction TPF followed by chemoradiation. The concurrent treatment after IC was platinum-based (carboplatin AUC1.5 weekly during St-RT) for patients in CR after IC and no-platinum-based (docetaxel 20 mg/mq weekly × 4 during AFX-C) for poor responders to IC. The trial was closed early due to slow accrual after only 145 patients out of the 300 planned had been randomized. No differences in OS (HR 1.09, 95%CI 0.59–2.03) and in PFS (HR 1.40, 95%CI 0.55–3.55) were observed.

The DeCIDE trial [22] was limited to patients with nodal stages N2–N3. All squamous cell carcinomas of the head and neck region, including unknown primary cancers, were eligible. The concurrent treatment was no-platinum-based in both arms: it was the combination developed by Chicago University consisting of docetaxel, 5FU, and hydroxyurea concomitant to hyperfractionated RT. In the experimental arm, only two cycles of induction TPF were administered before concomitant treatment. The trial did not achieve the planned accrual of 400 patients and the initial statistical hypothesis was re-

Table 1. Phase III trials comparing concomitant treatment vs induction TPF followed by concomitant treatment

Trial	Treatment arms	Planned accrual	Final accrual	Primary endpoint	TPF regimen	TPF cycles	ATB prophylaxis
PARADIGM [21]	Cisplatin/RT vs TPF × 3- > docetaxel/RT or carboplatin/RT	300	145	OS (p = NS)	T 75 mg/mq P 100 mg/mq F 1000 mg/mq/day d1- > 4 c.i.	3	No
DeCIDE [22]	DHF-RT vs TPF × 2- > DHF-RT	400	285	OS (p = NS)	T 75 mg/mq P 75 mg/mq F 750 mg/mq/day d1- > 5 ci.	2	No
TTCC trial [23]	Cisplatin/RT vs TPF × 3- > cisplatin/RT vs PF × 3- > cisplatin/RT	438	439	TTF PFS (p = NS)	T 75 mg/mq P 75 mg/mq F 750 mg/mq/day d1- > 5 c.i.	3	Yes
GSTTC trial [24•]	PF/RT vs CET/RT vs TPF × 3- > PF/RT vs CET/RT	420	421	OS (p = 0.03)	T 75 mg/mq P 80 mg/mq F 800 mg/mq/day d1- > 4 c.i.	3	Yes
GORTEC 2007.02 [25]	CbF-RT vs TPF × 3- > CET/RT	360	370	PFS (p = NS)	T 75 mg/mq P 75 mg/mq F 750 mg/mq/day d1- > 5 c.i.	3	Yes

Trial	Prophylactic G-CSF	G > 3 hematological toxicity and toxic deaths with IC					
		Neutropenia %		FN %	Anemia %	Platelets %	Toxic deaths %
PARADIGM [21]	Yes	nr		23*	nr	nr	0
DeCIDE [22]	Yes	36		11	0.7	2.9	2.9
TTCC trial [23]	Yes°	TPF arm	19	17	2.7	3.3	4.6§
		PF arm	34.6	1.9	0.6	5.8	2.5§
GSTTC trial [24•]	No	27.5		11	2.5	1	1

Table 1. (Continued)

Trial	Prophylactic G-CSF	G > 3 hematological toxicity and toxic deaths with IC				
		Neutropenia %	FN %	Anemia %	Platelets %	Toxic deaths %
GORTEC 2007.02 [25]	Yes	26	17	nr	nr	6.6

PF, cisplatin plus 5-fluorouracil; CET/RT, cetuximab/RT; CbF, carboplatin plus 5-fluorouracil; ATB, antibiotics; FN, febrile neutropenia
°After protocol amendment
*Cumulative data for IC phase + concomitant phase
§Total toxic deaths for IC + concomitant

calculated according to the 285 patients finally randomized. Overall response rate (ORR) after IC was 64%. No significant difference was observed in OS—primary endpoint—(HR 0.91; 95%CI 0.59–1.41) although a significant reduction in distant failure was reported in the IC arm ($p = 0.043$).

In both the PARADIGM and DeCIDE trials, excellent OS was observed in all treatment arms (> 70% at 3 years).

The first trial that reached the planned accrual was the Spanish Head and Neck Cancer Cooperative Group (TTCC) study [23]. Four hundred thirty-nine unresectable stage III–IV patients (TNM VII edition) were randomized to three cycles of high-dose cisplatin concurrent to St-RT (control arm) vs two sequential treatment arms with three cycles of induction PF or TPF followed by the same concomitant treatment. ORR to IC was 77.7% both after TPF and PF. No significant differences were observed either in time to treatment failure (TTF) or in PFS and OS according to the intention to treat (ITT) analysis. The 3-year OS was < 50% in all the arms. Interestingly, the per-protocol (PP) analysis showed a significant PFS advantage for the TPF arm vs cCRT alone (HR 0.72; 95%Cl 0.526–0.983; $p = 0.038$).

The second trial that completed the planned accrual was the GSTTC Italian phase II–III trial [24•]. It was a factorial 2 × 2 study limited to unresectable stage III–IV LAHNSCC (TNM VII edition) of the oropharynx, hypopharynx, and oral cavity. The trial had two different concomitant treatments: cCRT (two PF cycles during St-RT) vs CET/RT. Concomitant treatment alone was compared with three cycles of induction TPF followed by concomitant treatment. In the first part of the trial (the randomized phase II part), cCRT was the only concurrent regimen adopted [26]. A statistically significant advantage in CRs was observed in the IC arm (50% vs 21%, $p = 0.004$). Moreover, induction TPF did not compromise compliance with the concomitant treatment and fewer patients required surgery for residual disease after treatment completion ($p = 0.047$). The CET/RT arm was introduced in the phase III part of the trial, according to a reciprocal control study design, after publication of the pivotal phase III trial showing significant advantage for concurrent cetuximab vs RT alone.

Four hundred twenty-one patients were randomized to receive concomitant treatment alone (cCRT vs CET/RT) vs three cycles of induction TPF followed by cCRT or followed by CET/RT. The primary efficacy endpoint was OS of sequential treatment vs concomitant treatment. ORR after TPF was 76%. This was the first trial showing a significant OS benefit for IC (HR 0.74; 95%CI 0.56–0.97; $p = 0.031$; 3y OS 57.5% vs 46.5%) consistent with a significant improvement in CRs ($p = 0.0028$), PFS ($p = 0.013$), and LRC ($p = 0.036$). The 3y OS of the control arm was similar to the control arm of the TTCC trial (43%) and in line with that reported with concomitant treatment alone in other European studies [16, 27, 28]. Exploratory analysis of OS showed a higher effect of IC in non-oropharynx cancer (HR 0.66 vs 0.83) and in patients receiving CET/RT rather than cCRT after induction TPF (HR 0.57 vs 0.83). The unplanned analyses were only for explorative purposes and the data should be interpreted with caution. The HPV status was not available and a possible interaction between induction TPF and the type of concomitant treatment could not be excluded due to the lack of statistical power to evaluate the interaction.

The last completed trial was the GORTEC 2007.02 [25], limited to nodal stage > 2b (TNM VII edition). Three hundred seventy unresected patients (including laryngeal cancer), mainly HPV-negative, were randomly assigned to

receive three cycles of carboplatin + 5FU concomitant to St-RT vs three cycles of induction TPF followed by CET/RT. Unlike previous trials' results, ORR to TPF was only 44.5% and the rate of early deaths after TPF (6.6%) was the highest reported so far. Despite a significant advantage in distant control in the sequential arm (HR 0.62, 95%CI 0.40–0.95, $p = 0.03$), no significant differences were observed in PFS (HR 0.93, 95%CI 0.73–1.20; $p = 0.58$)—primary endpoint—LRC (HR 0.98, 95%CI 074–1.30; $p = 0.90$), and OS (HR 1.12, 95%CI 0.86–1.46, $p = 0.39$). The 3y OS was < 50% in both arms. About 30% of the patients in the control arm were not able to receive the three planned concomitant chemotherapy cycles, in line with literature data.

The 3y OS reported in European trials, whether with concomitant or sequential treatment, is typically lower than that reported in US trials. It is our opinion that US patients are selected for fewer comorbidities and better PS and these characteristics, together with the higher incidence of HPV-related cancer in US, could explain the different outcomes of US vs non-US trials.

Toxicity and compliance with sequential treatment

The phase III trials exploring the role of IC reported different toxicity profiles according to the TPF induction regimen used and the different concurrent treatments.

Toxicity of IC

Different TPF doses and numbers of cycles were adopted in addition to different supportive therapies for the prophylaxis of severe hematological toxicity and infections (Table 1).

The main differences in the TPF regimens concerned the doses of cisplatin and 5FU, while docetaxel schedule (75 mg/mq day1) was administered in all the trials. In the PARADIGM trial [21], a full dose of cisplatin (100 mg/mq day1) plus 5FU 1000 mg/mq/day as continuous infusion (c.i.) for four consecutive days was administered. The DeCIDE [22], TTCC [23], and GORTEC 2007.02 [25] trials adopted the TPF regimen developed by the EORTC in the TAX323 trial [14] with a reduced dose of cisplatin (75 mg/mq day1) and 5FU (750 mg/mq/day c.i. for 5 days). Three cycles were administered in the TTCC and GORTEC 2007.02 trials while only two cycles were administered in the DeCIDE study. In the Italian trial [24•], a modified TPF regimen [29] with cisplatin 80 mg/mq day1 and a lower total dose of 5FU (800 mg/mq/day c.i. for 4 days) was administered for three cycles. The ORR was 76%, similar to that reported with other TPF schedules.

Since the three TPF regimens were developed independently of each other and no phase III trials comparing the different schedules are available, they can all be considered adequate as IC.

It is well known that the TPF combination is burdened by high-grade hematological toxicity (Table 1), mainly neutropenia. The use of prophylactic antibiotic treatment (e.g., ciprofloxacin) is suggested after each cycle of TPF to decrease the risk of infections, while the use of prophylactic granulocyte colony-stimulating factor (G-CSF) is less established.

Because of toxicities resulting from induction TPF, this treatment modality should be administered in controlled clinical setting by highly experienced medical oncologists.

Compliance with concomitant treatment after IC

The critical issue of sequential treatment is the proportion of patients not able to start or to complete the concomitant treatment due to toxicities of IC (Table 2); however, it is difficult to draw accurate conclusions from these data because they are differently reported. Some trials reported the cumulative data of the sequential treatment (induction phase plus concomitant phase) while others reported the toxicity profile of the different phases of treatment separately.

The proportion of patients not receiving concomitant treatment after IC for any reasons (including PD, toxicities, deaths for any reasons, refusal) was 8.8% in the DeCIDE [22] trial, 10% in both the PARADIGM [21] and the Italian [24•] trials, 16.5% in the GORTEC 2007.02 study [25], and about 26% in the TTCC trial [23] (30.7% with TPF and 22.4% with PF).

Different proportions of early deaths after TPF were also reported: 1.4% in the PARADIGM [21] trial (one patient, not treatment related), 2.9% in the DeCIDE [22] study (four deaths, all treatment related), 1% in the Italian trial [24•] (two treatment-related deaths), and 3.8% in the TTCC trial [23] (5.2% after TPF and 2.5% after PF). The highest rate of early deaths, 6.6%, mainly related to neutropenia-associated infections, was reported in the GORTEC 2007.02 [25] trial. The GORTEC data is difficult to explain because both prophylactic antibiotics and G-CSF were administered during IC.

Toxicity to IC (not including early deaths) as a reason for not starting RT was not reported in three trials [21, 22, 25]. The proportion of patients not able to start RT due to toxicity was 2.4% in the Italian trial [24•] and about 12.2% in the TTCC study [23] (11.7% in the TPF arm and 12.8% in the PF arm).

Another critical issue is whether IC could compromise the compliance with subsequent concomitant treatment in terms of increased adverse events and treatment discontinuation.

The comparison of toxicity and compliance is possible in only three trials [19–21] because in the other two studies [18, 22], different concomitant treatments were adopted in the control arm. In the DeCIDE trial [19], the incidence of high-grade in-field mucositis and radiation-dermatitis during

Table 2. Proportion of patients not receiving concomitant treatment after IC

	PARADIGM [21]	DeCIDE [22]	TTCC trial [23] TPF	TTCC trial [23] PF	GSTTC trial [24•]	GORTEC 2007.02 [25]
Never started RT:	10%	8.8%	30.7%	22.4%	10%	16.5%
- PD	nr	nr	2.6%	5.7%	4%	5.5%
- Early deaths	1.4	2.9%	5.2%	2.5%	1%	6.6%
- Toxicity	nr	nr	11.7%	12.8%	2.4%	nr
- Others	nr	nr	11.1%	5.7%	2.6%	4.4%

PD, progressive disease

concomitant treatment was similar, irrespective of IC. Myelosuppression was significantly higher in pts receiving IC; however, the completion of concomitant treatment was similar in the two arms.

The TTCC trial [19] was the only study in which three cycles of concurrent high-dose cisplatin was adopted in all the treatment arms. Grade 3–4 in-field mucositis was more frequently reported in the IC arms (49% in the TPF arm and 50% in the PF arm vs 33% in the cCRT arm) while the incidence of radiation-dermatitis was not reported. Renal dysfunction related to cisplatin is another issue that could affect the completion of the concomitant treatment. The planned cisplatin total dose was 300 mg/mq in the control arm vs > 500 mg/mq in both sequential arms (IC + concomitant). Grade 3–4 renal dysfunction was reported in a significant number of patients in all the arms: 8.4% in the TPF arm, 3.1% in the PF arm, and 5.1% in the cCRT arm. Of the patients in the IC arms, 15% discontinued concomitant treatment (17% in the TPF arm and 13% in the PF arm), while 18% stopped cCRT before completion in the control arm. Moreover, about 31% of the patients received < 3 concomitant cisplatin cycles: 40.5% in the TPF arm, 34% in the PF arm, and 19.5% in the cCRT arm. These data confirm the suboptimal compliance to three cycles of concomitant cisplatin high dose, especially in patients receiving cisplatin-based IC.

The better compliance to concomitant treatment reported in the Italian trial [20] vs the Spanish TTCC trial [19] might be attributable to the schedule and doses of TPF and to the concomitant regimens. During the concomitant phase of the treatment, there was no increase in incidence of G3–4 in-field mucositis and radiation-dermatitis (34.5% vs. 41% and 14% vs. 15%, respectively) in patients receiving IC. The maximum grade of renal toxicity during the concomitant phase of the treatment was G2 in both arms (three patients). It should be noted that the cisplatin total dose in the sequential arm was 400 mg/mq vs > 500 mg/mq in the Spanish trial. The proportion of patients able to complete the planned RT was 93% in both arms and the completion of the planned concomitant systemic treatment was 88% in the control arm and 85% in the sequential arm.

Who is the ideal candidate for sequential treatment?

We present our personal considerations regarding the selection of patients for sequential treatment, in accordance with our clinical practice. Two clinical cases will help us explain our point of view.

The first (Fig. 1a) is a 51-year-old-man with an HPV-positive oropharynx cancer stage cT2N2b (stage IV, TNM VII ed). He is a current smoker (10 pack/year) with no cancer-related symptoms, no comorbidities, and an ECOG PS 0. The MRI of the head and neck region reveal a low tumor burden both on primary site and on the neck. He is not a good candidate for IC.

The second case (Fig. 1b) is a male (54-year-old) with HPV-unrelated oropharynx cancer, stage cT4aN2c (stage IV, TNM VII ed). He has several cancer-related symptoms: pain, dysphagia, weight loss of 7% in the last 6 months. He is a heavy smoker (25 pack/year) with no relevant comorbidities

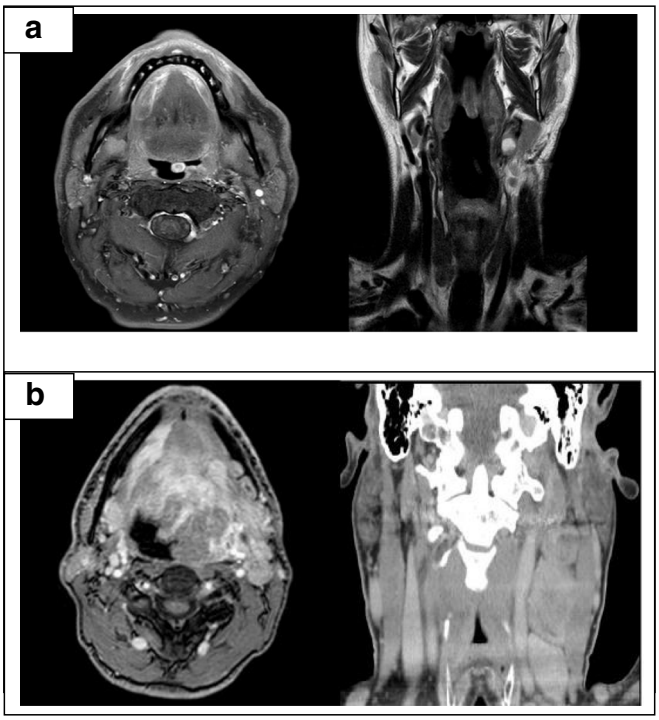

Fig. 1. Oropharynx cancer, stage cT2N2b-TNM VII ed (**a**) and oropharynx cancer, stage cT4aN2c-TNM VII ed (**b**).

and an ECOG PS of 1. In our opinion, this patient is a good candidate for treatment intensification with IC.

Our proposal is to consider IC for patients with good ECOG PS, no relevant comorbidities, heavy cancer-related symptoms, and high tumor burden (both on primary site and/or on the neck) because of the ability of TPF to positively affect both loco-regional and distant control. Molecular and biological characteristics could be useful to better select patients as candidate for treatment intensification. HPV status can also be considered when selecting patients with a poor prognosis. Since HPV-related cancers have better prognosis, negative HPV cancers could benefit more from intensive treatments.

Unanswered questions and future directions

In addition to previous considerations, several questions are still open.

If IC is planned, which is the best concomitant treatment to be administered after IC? This was the primary endpoint of the non-inferiority TTCC 2007-01 trial, not yet published [30]. The trial compared cCRT (three cycles of high-dose cisplatin concurrent to St-RT) vs CET/RT in 407 unresectable stage III–IV patients (TNM VII ed) not progressed to induction TPF. Preliminary data did not show significant differences in OS (primary endpoint), PFS, and LRC. In-field high-grade toxicities were more frequently reported in the CET/RT arm (both mucositis and radiation-

dermatitis) while higher incidence of systemic toxicity was reported in the cCRT arm. These preliminary data are in line with the results of the TREMPLIN study, a randomized phase II trial with similar study design [31] involving resectable patients candidate for larynx preservation.

Immunotherapy as a potential intensification strategy

ICIs are emerging new class of drugs with a strong rationale for combination with chemotherapy and RT. Several clinical trials are evaluating the role of ICIs added (concurrently and/or sequentially) to definitive loco-regional treatment. No phase III trials have been yet completed in LAHNSCC; however, interesting preliminary safety and efficacy data come from phase I–II trials.

Pembrolizumab (200 mg q3w) was added to cCRT (weekly cisplatin concurrent to St-RT) in a recent safety trial [32]. The interim analysis on the first 27 patients showed that pembrolizumab neither compromised the completion of the concomitant treatment nor increased the expected incidence of high-grade toxicities. Discontinuation of pembrolizumab due to immune-related adverse events was 11%. Complete responses (CRs) at the end of treatment were quite high, 78% in all the patient population and 85% in HPV-positive oropharynx cancer.

The RTOG 3504 trial [33, 34] sequentially enrolled 29 patients to receive nivolumab plus cCRT or nivolumab plus CET/RT. In addition, nivolumab was sequentially administered after the completion of the concomitant treatment. No safety concerns were observed and preliminary promising outcome justifies the ongoing phase III trial.

The role of pembrolizumab and nivolumab as pre-operative treatment has been evaluated in non-randomized trials [35, 36]. No serious complications or treatment-related adverse events or unexpected surgical delays were reported. Tumor shrinkage was quite high before surgery with possible implications for the post-operative treatment plan.

Conclusions

Concomitant platinum-based cCRT is the standard of care for LAHNSCC unsuitable for radical surgery. CET/RT is an alternative treatment option for patients unfit for concurrent cisplatin.

Adding cetuximab to cCRT failed to improve OS in two phase III trials. No definitive conclusions regarding the role of IC as an intensification strategy can be drawn due to the heterogeneity of the trials, difficulty in interpreting the data, and inconclusive results, so that confirmation trials are needed. Although sequential treatment cannot be considered a standard of care, it should be a treatment option for selected patients at poor prognosis. Accurate patient selection and multidisciplinary evaluation are mandatory for the identification of those patients who will potentially benefit from the treatment. After induction TPF, three cycles of concurrent cisplatin high dose are not recommended due to toxicity concerns. Both IC and concomitant treatments should be administered by medical oncologists and radiation oncologists with considerable experience in the

treatment of head and neck cancer to minimize the adverse events related to treatment.

Immunotherapy is a new treatment option in recurrent/metastatic disease. Randomized trials evaluating its role in LAHNSCC are ongoing. Several questions are still open on the role of ICIs with regard to the timing and length of administration; moreover, predictive markers are needed and associations with conventional treatment need to be tested.

Compliance with Ethical Standards

Conflict of Interest
Maria Grazia Ghi and Adriano Paccagnella declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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