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Review

Induction chemotherapy in head and neck cancers: Results and controversies

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ABSTRACT

Standard treatment for locally advanced head and neck squamous cell carcinoma (LAHNSCC) consists mainly of concurrent chemoradiation (CCR) but induction chemotherapy (IC) by docetaxel-cisplatin-fluorouracil (TPF), followed by CCR, is a strong option. Comparative trials suggest that IC and CCR are equivalent, and some trials suggest superiority of IC, whereas none shows inferiority. IC might have less interest in oropharyngeal cancer (more often linked to HPV infection). When functional laryngeal preservation is the patient's priority, essays strongly suggest that IC is the best treatment. There is little data about a less toxic regimen of IC, but several schemes are promising and need to be developed. An early selection of responders to IC by metabolic imaging must be considered. Intensification attempts with cetuximab were too toxic and unsafe, but trials with immunotherapy are ongoing to enhance TPF efficacy. After IC, CCR either with cetuximab or cisplatin seems to be equally effective.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide, with over 650,000 new diagnoses every year [1]. HNSCC are locally advanced (T3, T4 or N+, LAHNSCC) in 60% of newly diagnosed patients. For resectable disease, concomitant chemoradiation (CCR) and surgery followed by radio(chemotherapy) are both effective. The choice of treatment depends largely on the tumor's localization and the schools. For inoperable diseases, CCR remains the standard but induction chemotherapy (IC) followed by surgery and/or CCR is a strong option. In this review we will focus on IC: rational, type, results, controversies and future directions.

Rational and standard induction

Induction chemotherapy can eradicate micro metastases and thus increase progression free survival (PFS) and overall survival (OS) in patients with LAHNSCC. It can predict the tumor's sensitivity and can help decide between radical surgery and CCR [2], even if this assumption lacks definitive proof. Indeed, of the 24 out of 173 patients with laryngeal cancer who did not respond to IC in the RTOG 91–11 [3] (detailed later), 11 were cured by radiotherapy, and in a retrospective study there did not seem to be a difference in OS or PFS between patients who refused total laryngectomy after no response to IC and those who had radical surgery before radiotherapy [4]. Finally, IC can decrease the tumor volume and make it operable when surgery was formerly too risky or too mutilating, in order to enhance quality of life.

The MACH-NC meta-analysis showed a significant benefit of IC if cisplatin and fluorouracil were used [5] and for more than 30 years, standard treatment for IC was cisplatin 100 mg/m^2 (on day one) and fluorouracil 1000 mg/m^2 per day, administered as a continuous 24 h infusion for five days, every three weeks (PF).

Since paclitaxel and docetaxel demonstrated activity, they have been included in induction chemotherapy regimens. Two phase III trials compared docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 (or 100 mg/m^2) + fluorouracil 750 mg/m^2/d for five days (TPF) versus PF every three weeks in HNSCC: TPF increased PFS (11.0 months versus 8.2 months; $p = 0.007$ in the first study with unresectable tumors and 38 months vs 13.2; $p = 0.011$ in the second one with resectable and unresectable tumors) and OS (18,8 months vs 14.5; $p = 0.02$ and 71 months vs 35; $p = 0.014$) [6–8]. Moreover, due to lower doses of cisplatin and fluorouracil in the TPF scheme, severe adverse events were less frequent in the TPF group than in the PF group. A meta-analysis of five randomized trials with 1772 patients showed that TPF (with paclitaxel or docetaxel) was associated with significant reductions of progression, locoregional failure, and distant failure if compared with PF [9]. The hazard ratio of death was 0.79 (95% CI 0.70–0.89; $p < 0.001$; absolute benefit at 5 years: 7.4%). So, when induction is

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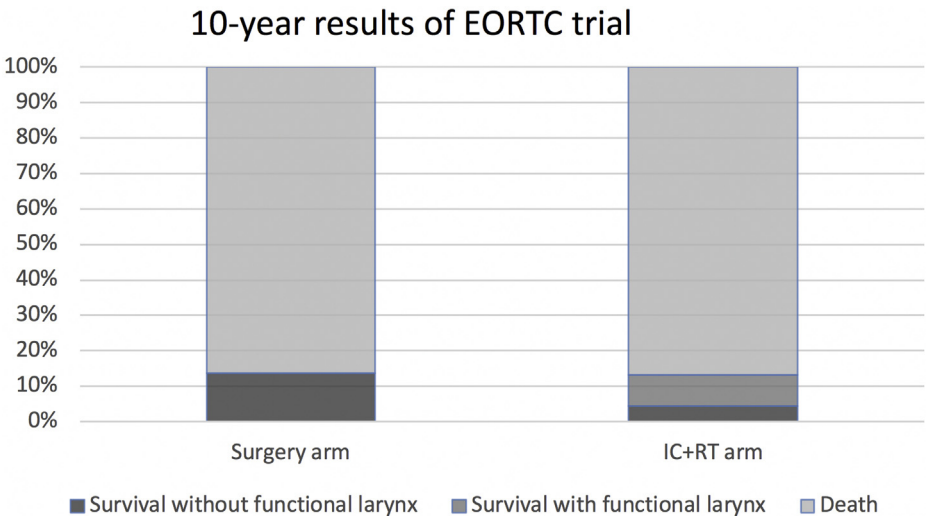

Fig. 1. 10-year results of EORTC trial for larynx preservation.

considered, the standard treatment is TPF.

A gold standard for larynx preservation?

Total laryngectomy cures advanced hypopharynx or larynx cancer but is mutilating. In 1991, a study demonstrated that three cycles of PF followed by radiotherapy allowed a survival rate similar to total laryngectomy (2-year survival of 68% in both groups, p = 0.9846), with more frequent local recurrences and fewer distant metastases [10]. Larynx was preserved in 64% of the patients treated by IC. A European study confirmed equivalent results with surgery and IC in hypopharyngeal squamous cell carcinomas with a 10-year survival rate of 13.8% and 13.1% respectively [11]. In the IC arm, the 10-year survival rate with a functional larynx was 8.7% (see Fig. 1).

The RTOG 91–11 trial compared CCR with cisplatin q3w and RT alone with the induction PF approach in 520 patients with stage III or IV glottic or supraglottic cancer. High-volume T4 (primary invasion > 1 cm into the base of tongue or penetration through cartilage) were excluded. The long-term results showed that CCR significantly improved the larynx preservation rate over IC followed by RT (HR 0.58; 95% CI 0.37–0.89; p = 0.0050) and over RT alone (p < 0.001) [12]. However, there was a trend, although not significant, concerning laryngectomy-free survival with 28.9% at 10 years for the induction approach versus 23.5% for the concomitant approach (see Fig. 2). It was the same with OS, with 5- and 10-year estimates of 58% and 39% for induction and 55% and 28% for concomitant, respectively. After about 4.5 years, the curves begin to separate, favoring induction, although the difference is not statistically significant. The increase of deaths in the CCR arm is not related to cancer deaths and could be related to intercurrent deaths due to a dysfunctional larynx (pneumonitis for example). The moderns radiation techniques could decrease this toxicity.

After the demonstration of superiority of TPF over PF as IC, this new scheme was studied.

The GORTEC 200–2001 trial which compared induction by PF with TPF in 213 patients for organ preservation (stage III or IV larynx and hypopharynx) confirmed that TPF increased larynx-preservation and larynx dysfunction-free survival with possibly less toxicity [13]. The 5- and 10-year larynx dysfunction-free survival rates were respectively 74.0% (95% CI 0.64–0.82) vs. 58.1% (95%CI 0.47–0.68) and 70.3% (95%CI 0.58–0.8) vs. 46.5% (95% CI 0.31–0.63, p = 0.01) in the TPF versus PF arm. Despite a trend for TPF, overall survival, disease-free survival, and locoregional control rates were not different, but TPF allowed significantly fewer grade 3–4 late toxicities of the larynx (9.3% vs 17.1%, p = 0.038).

Those results were confirmed by the TAX324 trial for advanced

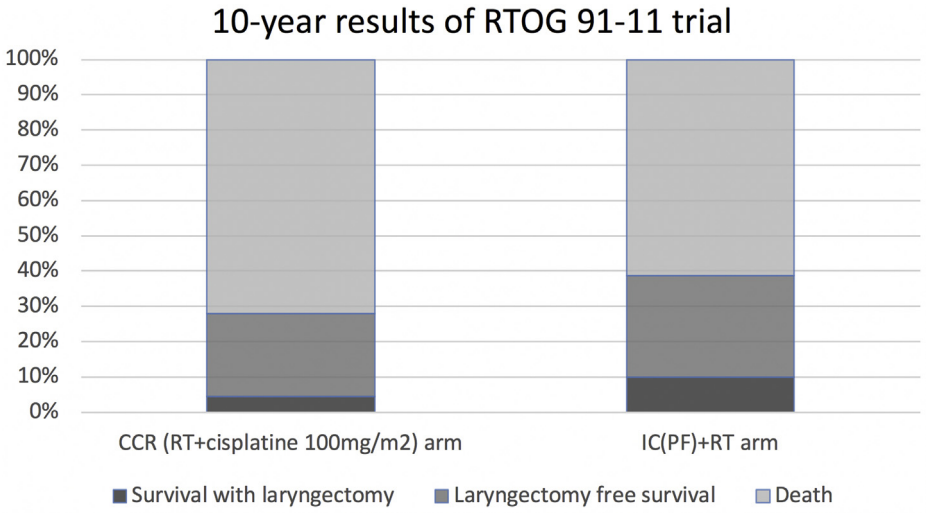

Fig. 2. 10-year results of RTOG 91–11 trial for larynx preservation.

Table 1
Direct comparisons in phase III trials.

Trial	Trial scheme	Population/follow-up	Results	Bias and weaknesses
DeCIDE trial [16]	TPF + CCR (with fluorouracil, docetaxel and hydroxyurea) versus same CCR	- 285 patients with N2 and N3 HNSCC - 30 months follow-up	No statistically significant difference in OS (HR, 0.91; 95% CI, 0.59–1.41), in favor of IC Strong trend in OS for high risk tumors (N2c and N3).	Lack of power: - only 285/400 patients included - OS higher than expected
PARADIGM trial [17]	TPF + CCR (with carboplatin or docetaxel) versus CCR (with two cycles of cisplatin 100 mg/m^2)	145 patients with high risk HNSCC: - stage III or IV, - N2 or N3 (except N2 T1). - three years follow-up	No statistically significant difference in OS (HR, 1.09; 95% CI 0.59–2.03), in favor of IC	Lack of power: - only 145/300 patients included - OS was higher than expected in the control arm
GORTEC 2007–02 trial [19]	TPF + CCR (with cetuximab) versus CCR (three cycles of carboplatin + fluorouracil)	370 patients with high risk HNSCC: - stage III or IV - N2b/c and N3 - 31 months follow-up	- No statistically significant differences in PFS and OS (HR, 1.10; 95% CI 0.84–1.45) in favor of CCR - Higher distant free metastasis survival in TPF arm (HR, 0.62; 95% CI 0.40–0.95)	CCR scheme was not a standard (carboplatin + fluorouracil)
TTCC trial [20]	TPF + CCR (three cycles of cisplatin 100 mg/m^2) versus PF + CCR versus CCR alone	439 patients with stage III and IV HNSCC - 24 months follow-up	- No statistically significant differences in PFS (14,6 months in TPF + CCR; 14,3 months in PF + CCR and 13,8 months in CCR alone	- Many patients where ECOG 1 regarding to the other trials. - Many high-volume tumors (T4)

hypopharyngeal and laryngeal cancers with an operable disease. Laryngectomy-free survival was significantly greater with TPF (HR: 0.59; 95% CI: 0.37–0.95; P = 0.030) [14], with a strong trend in OS for TPF.

These trials strongly suggest that induction chemotherapy with TPF should be a standard of treatment for functional laryngeal preservation.

The definitive response will come from the GORTEC phase III study [15] that compares exclusive CCR with three cisplatin 100 mg/m^2 to TPF followed by the same CCR.

Induction for inoperable patients or for oral cavity and oropharynx cancers: results and controversies

Direct comparisons in phase III trials

Standard treatment remains CCR and several phase III trials compared induction followed by CCR to exclusive CCR with discordant results (see Table 1).

Two American randomized phase III trials did not show any significant superiority of the IC + CCR strategy versus CCR alone [16,17], but they are methodologically questionable. Indeed, they included only half of the planned patients (285/400 and 145/300) and the observed OS was higher than expected so the statistical power was too weak and could not lead to definitive conclusion. The only argument in favor of IC was the diminished metastatic failure in one of the trials [16]. Of note, in the DECIDE trial [16], there was a strong trend in OS in favor of IC in high-risk tumors (N2c and N3). This trend was also suggested in a retrospective analysis that showed a benefit in OS in favor of TPF vs CCR for high risk tumors (N2b, N2c and N3) with a not reached OS vs 14 months [18].

A French study randomized 370 inoperable patients, at least N2b, to receive exclusive CCR (70 Gy potentiated by three cycles of carboplatin and fluorouracil) or IC followed by RT potentiated by cetuximab. In this population, the response rate was weak with induction (44.5%) and 7% of toxic deaths were deplored during IC. Finally, there was no difference between the two arms with a 2-year PFS of 40% (less than the 45% expected for the control arm). Interestingly, survival without metastases was significantly better with induction (HR 0.62 (IC95% 0.40–0.95) p = 0.03) [19].

A phase III Spanish trial [20] compared IC, either three TPF (155 patients) or three PF (156 patients), followed by CCR (potentiated by three cisplatin at 100 mg/m^2) or the same exclusive CCR (128 patients). Out of 311 patients in the IC arms, only 220 (70%) were irradiated. The reasons for that were: 13 deaths, 38 toxicities, 13 progressions, 27 other reasons. In the intent to treat analysis, no significant difference was observed between the three arms. But in the per-protocol analysis, the comparison of TPF + CCR versus CCR showed a significant benefit of IC + CCR for PFS (HR 0.72; 95% CI 0.53–0.98; p = 0.03) with a non-significant trend for OS (35.6 months (95% CI 24.2–51.4) vs 29.4 months (95% CI 18.9–45.4). Even if we cannot exclude a lead time bias by selection of patients with a better prognosis, these results suggest that the sequential approach might offer better results for patients that can tolerate it. Of course, predictive markers are needed in order to determine which patients could respond to and tolerate IC before choosing the treatment's sequence.

The last trial followed a phase II study that suggested benefit of IC followed by CCR vs CCR alone. It randomized 421 patients with stage III-IV HNSCC of the oral cavity, oropharynx and hypopharynx to one of four treatments: CCR (by cisplatin/fluorouracil two cycles), radiotherapy with cetuximab (CET/RT), three cycles of TPF followed by the same CCR or by CET/RT [21]. For analysis, data of the two IC arms and of the two exclusive RT were pooled. Results are significantly in favor of IC: complete response 42.5% vs 28% (p = 0.003), median PFS 30.5 months vs 18.5 (HR 0.72; 95%CI 0.56–0.93; p = 0.013) and especially median OS 54.7 months vs 31.7 (HR 0.74; 95%CI 0.56–0.97; p = 0.031), even in multivariate analysis. Since we cannot rule out in

the exclusive arms that cetuximab is inferior to platin-based chemotherapy, we again cannot draw definitive conclusion, especially since in subgroup analysis there is no significant difference for patients treated only by platin-based chemotherapy and not cetuximab. Moreover the addition of the 101 patients of the phase II study in the phase III study could decrease the confidence in the statistical analysis.

So, in direct comparisons, no study definitively concludes to the superiority of one strategy: IC seems non-inferior to exclusive CCR and remains a strong option. In all of these studies, it seems that induction has less interest in oropharyngeal cancer (more frequent in the American trials and more concerned by the HPV infection). Of note, for patients with high risk of metastases, IC could be a positive option.

Indirect comparisons by meta-analysis

Several meta-analyses have been performed in order to demonstrate a potential difference between IC and CCR. Some demonstrated a significant lower metastasis rate of about 7% [22–24] or a significant increase of PFS [25,26] but none demonstrated any significant benefit in OS despite a trend in favor of IC [22,23,25,27]. On the contrary, the last actualization of the MACH-NC analysis with more than 100 trials and 19,248 patients showed in a direct comparison between IC and CCR that OS was significantly better with CCR (HR 0.84 [95%CI 0.74–0.95], p = 0.0007) [28]. But, the major issue of these meta-analyses is the type of IC that include non-platin-based chemotherapy, platin-based chemotherapy without docetaxel and TPF. Today we have no meta-analysis focusing only on trials of IC by TPF and again no definitive conclusion can be drawn.

Less toxic induction chemotherapy attempts and better selection

Two major issues limit IC when compared with CCR: it could compromise the following CCR and its own toxicity (7% of death rate reported in one phase III study [19]).

None but one of the five phase III mentioned above use standard potentiation by three cisplatin 100 mg/m^2 after induction. It showed that if 80.5% of the patients of the CCR arm received the three cycles of cisplatin, they were only 59.4% in the TPF arm [20]. Another study showed that only 22% of the patients were able to be treated by CCR with cisplatin > 200 mg/m^2 after three cycles TPF [29]. That's why new less toxic schedules were explored.

Since modified TPF (docetaxel and cisplatin at 40 mg/m^2 each on day 1, leucovorin 400 mg/m^2 followed by a bolus of fluorouracil at 400 mg/m^2 then 1000 mg/m^2/day, day 1-day 2, every two weeks) increased OS with less toxicity in gastric cancer compared to TPF, it was tested in HNSCC for patients unfit for TPF (PS > 1, Age > 70 years, cardiac failure, high loss of weight…) in a retrospective study [30]. In this frail population, only 8% febrile neutropenia and 4% death was observed and modified TPF allowed 83% responses and 81% of patients could be irradiated. A randomized study of the GORTEC is currently evaluating modified TPF compared to TPF for fit patients as IC.

Another small monocentric retrospective study evaluated dose-dense modified TPF in 11 patients: docetaxel 40 mg/m^2, cisplatin 40 mg/m^2 or carboplatin AUC2 and fluorouracil (400 mg/m^2 bolus then 1000 mg/m^2 in 96 h), bi-monthly [31]. One patient had febrile neutropenia, no grade 3–4 gastrointestinal toxicity was reported and response rate reached 90% (30% complete response).

A retrospective study compared 53 patients treated in a single institution by carboplatin AUC2 and paclitaxel 135 mg/m^2 every seven days for six weeks (CP) to 90 treated by TPF [32]. In multivariate analysis, locoregional control was better in the CP arm (HR 0.27; p = 0.04), but not PFS (p = 0.15). Renal toxicity was higher with the TPF arm and neutropenia occurred more often with CP.

These studies are too small to conclude but suggest that new modalities of IC are possible in order to decrease toxicity. The challenge is to assess if efficacy could be maintained.

Since IC could be a treatment of choice for a large number of patients, a current challenge is to select these patients. A phase II tried to modify TPF and quickly select patients with a LAHNSCC who will benefit from it [33]. The split-dose TPF was a 3-week cycle with docetaxel 30 mg/m^2, cisplatin 40 mg/m^2, fluorouracil 2000 mg/m^2 during 24 h at days 1 and 8. It was administered to 54 patients with locally advanced and resectable cancer of the oral cavity or oropharynx. In responders (radiological response > 30%, 70% of patients), IC was continued with an additional two cycles more before surgery and CCR. In non-responders, surgery was immediately performed before CCR. All the patients benefited from surgery and major radiotherapy protocol deviations did not occur. As expected, 24 months PFS and OS were higher in responders (88.5% vs 60.6% and 97.3% vs 73.7% respectively).

Fluorouracil is probably the less efficient drug in TPF and has an important toxicity, so various schedules were developed without it.

A randomized, multicenter phase II study [34] enrolled 92 patients with LAHNSCC to receive three cycles of docetaxel and cisplatin with or without cetuximab (TP and TPE) as induction chemotherapy. Patients in the TPE arm received CCR with cetuximab and cisplatin whereas patients in the TP arm received cisplatin alone. In intention-to-treat analysis, the 3-year OS was not increased by cetuximab (88% vs 74%, p = 0.31), possibly because cetuximab was responsible for a diminished treatment completion (67% vs 77%). In per protocol analysis (IC + CCR completed, 67% in the TPE arm vs 77%), the 3-year OS was significantly higher with cetuximab (94% vs 73%, p = 0.045).

A single arm essay using the same IC with TPE and CCR with cisplatin and cetuximab [35] had similar results: 3-year PFS 70% (95%CI 53–82%) and 3-year OS 74%. Again, toxicity was important with frequent grade 3/4 toxicities, including febrile neutropenia (10%), mucositis (54%), dysphagia (48%), and hypomagnesemia (39%). So replacing fluorouracil by cetuximab is toxic and does not show clear evidence of superiority.

A Phase II trial [36] included 47 patients with LAHNSCC to receive bi-monthly six cycles of paclitaxel 135 mg/m^2 and carboplatin (AUC2) with cetuximab. CCR was potentiated with cisplatin. The 3-year PFS and OS rates were 87% (95%CI 78–97%) and 91% (95%CI 84–99%), respectively. Excepted for mucositis (77% grade 3–4), skin rash (45% grade 3–4) and 21% non-febrile neutropenia, this scheme was well tolerated and a majority of the patients completed induction as planned per protocol.

Two other phase II studies with 63 and 30 patients confirmed that the combination of carboplatin, paclitaxel and cetuximab seems safe and promising [37,38].

PET-scans could be an interesting option to select responders to IC. A French prospective essay evaluated the metabolic response after two cycles of TPF in 15 patients with non-surgical LAHNSCC. FDG PET-scans were performed before and after two cycles of TPF, and SUV-max comparison was performed between the two exams. Median PFS was 18.9 months for metabolic responders (decrease of SUV-max > 25%) and 10.2 months for metabolic non-responders (p = 0,0014) [39]. Those results were confirmed in a 26 patients cohort with PET-scan evaluation after one TPF course [40]. Early identification of non-responders would possibly have avoided ineffective treatment and many unnecessary adverse effects.

So a less toxic schedule and a better and earlier assessment of effectiveness of IC are probably a promising way and deserve additional investigations.

Can TPF be intensified?

Despite its toxicity, some studies tried to intensify TPF. A first phase II trial in 50 patients added weekly cetuximab to TPF (C-TPF) for four cycles [41]. Response rate was similar to TPF at 86% (95% CI: 73–94) but toxicity was highly increased with febrile neutropenia (24%), grade 3–4 diarrhea (20%) and grade 3–4 mucositis (14%). On the contrary,

another study in Taiwan suggested on the contrary the feasibility of two C-TPF, with similar grade 3–4 leucopenia (26% and 28% for TPF and C-TPF, respectively). Patients were clearly different from western countries (young, non-drinker, non-smoker) [42].

A German study compared C-TPF to TPF but, due to the toxicity, the protocol was amended to suppress fluorouracil and then to compare C-TP to TP in 173 patients [43]. No significant difference was observed between the two arms in 2-year OS (overall or with functional larynx). Since the standard is TPF no conclusion can be drawn.

Because of the high toxicity of C-TPF, docetaxel was replaced by nabpaclitaxel (100 mg/m^2) and fluorouracil shortened at day 1–3 in a phase II trial in 30 patients [44]. This promising schedule showed 53% complete response and did not adversely affect delivery of definitive CCR (81% of patients did receive three cycles of cisplatin 100 mg/m^2).

Since immunotherapy with anti-PD1/PDL1 demonstrated efficacy in recurrent HNSCC with an excellent tolerability, these checkpoint inhibitors are currently tested in combination with TPF and can provide a new type of intensification in induction.

Which potentiation after induction?

To this day, there is no standard approach for radiotherapy after IC: on its own? With cisplatin? With cetuximab?

A French phase II study tried to answer this by comparing radiotherapy (70 Gy) with concurrent cisplatin q3w with concurrent cetuximab after three TPF for organ preservation (stage III or IV larynx/hypopharynx) [45]. The primary end point was larynx preservation at three months, and there was no significant difference (95% and 93%, respectively), and it was similar for OS at 18 months (92% and 89%, respectively). Local failures were more numerous in the cetuximab group. Radiotherapy with cisplatin was more toxic since only 42% of patients received the three planned cycles whereas 71% of the patients in the cetuximab group received the seven planned injections.

The interim analysis of a phase III study with the same approach was presented with the same approach [46]: 519 patients with inoperable stage III/IV HNSCC received TPF. If it was tolerated and there was no progression, they were randomized (4 0 7) to receive potentiation by either cisplatin or cetuximab. Because of the excellent results of IC, this trial didn't reach sufficient event rates and only interim data were presented. In intention-to-treat analysis, median OS was 42.2 months (95%CI 33.7–52.4). There was a non-significant trend for cisplatin: 63.6 months (95%CI 43.6–77.5) vs 47.1 months (95%CI 33.7-NA) for OS (p = 1.17) and 37 months (95%CI 23–62.9) vs 20,7 months (95%CI 15.3–31.1) for PFS (p = 1.20). More time is needed to see if this trend in favor of cisplatin is confirmed and becomes significant.

Induction and human papilloma virus (HPV)

In Europe, almost 40% of HNSCC are HPV related [47]. Several essays showed the higher chemosensitivity and radiosensitivity of HPV induced HNSCC [48].

In a retrospective subset analysis of an EORTC phase III essay for IC (PF versus TPF), 14% of evaluable samples were p16+ and 25% were HPV-DNA+. The analysis showed no statistical evidence of predictive value of HPV/p16 status either for PFS (P = 0.287) or OS (P = 0.118). Those results do not justify deintensifying TPF for PF in HPV related HNSCC [49].

A subset analysis of the American National Cancer Database with almost 15,000 patients with oropharyngeal cancer was conducted to evaluate HPV status impact. HPV status was known in 35% of patients, and it was positive for 55% of them. HPV-positivity was associated with a better 3-year OS with a HR of 0.46 (95% CI 0.35–0.60, p < 0.001). There was no statistical difference between IC and CCR with HPV-positive patients (HR 0.96; 95% CI 0.72–1.27; p = 0.761). However, when further restricting the cohort to high risk (T4 and/or N3 disease) HPV-negative tumors (n = 219), IC treatment was significantly associated with higher 3-year OS (HR 0.63; 95% CI 0.0–1.0; p = 0.048). Further analyses is needed [50].

ECOG 1308 trial [51] suggested that tumor response rate to IC with three cycles of cisplatin, paclitaxel and cetuximab could be used to select patients for de-escalation radiation dose in HPV related HNSCC. Patient with a complete response rate after three cycles of IC (70% of them) received CCR with 54 Gy potentiated with weekly cetuximab, those without a complete response received 69,3Gy with weekly cetuximab. Indeed, outcomes where excellent for responders, with 2-year PFS and OS rates of 80% and 94%, respectively. Moreover, radiation dose reduction improved swallowing and nutritional status.

Conclusion

Induction chemotherapy has several aims for LAHNSCC. It can decrease the tumor volume in order to make a tumor resectable. Moreover, its goal is to eradicate micrometastases and reduce locoregional failure. The standard treatment for induction is TPF. When a treatment for preservation of laryngeal function is propounded, chemotherapy with TPF has shown its superiority with a high level of evidence. Outside larynx preservation, CCR is the standard and IC + CCR remains an option. But, in direct comparisons, no study definitively concludes to the superiority of any strategy and IC seems to be non-inferior to exclusive CCR. Meta-analysis cannot draw any definitive answer because none is focused on trials using TPF for IC. Further evaluations are needed and today IC is a reliable option [52,53].

Because of the high toxicity of IC, additional investigations are necessary to design less toxic schedules having the same efficacy. Various ways are explored to identify non-responders and spare them from accrued toxicities and an early assessment of efficacy by PET-scan is one of them. On the contrary, attempts to intensify TPF with cetuximab in order to increase efficacy were highly toxic. Promising schemes with nab-paclitaxel or immunotherapy should increase the choice of TPF for a selected population.

After a treatment by IC, essays didn't highlight any superiority in using cetuximab or cisplatin for CCR, even if CCR with cetuximab seems to be well tolerated.

Declaration of Competing Interest

None declared.

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