Induction chemotherapy in head and neck cancer: a new paradigm

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Five hundred and fifty thousand new head and neck cancer cases are diagnosed each year worldwide. They are mostly locally advanced squamous cell carcinoma with a poor prognosis in terms of locoregional and distant failure. A major challenge for patients with locally advanced squamous cell carcinoma is to achieve a high cure rate while preserving functions. Treatment strategies are designed according to the disease stage, primary site, operable status, patient age, and performance status. Surgery, radiation therapy, chemotherapy, and more recently molecular-targeted therapies are part of these strategies, but their sequence remains to be defined. Over the last 30 years, induction chemotherapy has attained an important position in the management of patients with locally advanced squamous cell carcinoma, particularly since the introduction of taxanes. The decision to deliver induction chemotherapy (and its intensification) must be considered in the light of other treatments aiming at better locoregional control (normofractioned radiotherapy, accelerated or hyperfractionated radiotherapy, addition of concurrent chemotherapy, or of targeted therapy) with or without adjuvant treatment. This review summarizes the rationale, these data, and perspectives on induction chemotherapy-based strategies. *Anti-Cancer Drugs* 22:613–620 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Over 550 000 new head and neck cancer cases are diagnosed each year worldwide. The reported incidence in the United States was approximately 48 000 patients [1], 76 000 in Europe, [2] and 20 000 in France [3]. There is a wide geographical variability for this disease incidence in high-risk countries, and especially for laryngeal cancers in southern Europe (France, Italy, and Spain) [4].

Tobacco and alcohol consumption are the most important risk factors for head and neck cancers, particularly for the oral cavity, oropharynx, hypopharynx, and larynx [5]. Recently, exposure to human papillomavirus (HPV) has been increasingly reported in association with oropharyngeal cancer [6], regardless of the use of tobacco and alcohol, and without evidence of synergy between exposure to HPV and use of tobacco and alcohol. HPV-positive oropharyngeal cancers may represent a distinct disease entity that is causally associated with HPV infection and that is associated with an improved prognosis. This survival improvement was indicated by several studies [7–9].

Most of these patients present with a squamous cell carcinoma (SCC) and approximately two-thirds of patients with SCC present with locoregionally advanced SCC (LASCC) [10]. Unfortunately, 30–40% of these patients die of this disease [11].

A major challenge for patients with LASCC is to obtain a high cure rate while preserving function, as pharyngolaryngeal structures are involved in nutrition, communication, and breathing. Treatment strategies are designed according to tumor stage, primary site, operable status, patient age, and performance status. The use of new imaging modalities such as MRI or PET-computed tomography scanning makes it possible to fine-tune the tumor node metastasis classification [12] and subsequently to better select the most appropriate treatment. Surgery, radiation therapy, chemotherapy, and more recently molecular-targeted therapies are the main therapy tools for LASCC, but their sequence remains unclear, especially for organ preservation strategies, and for unresectable tumors. Therefore, the multidisciplinary approach is crucial. Systemic therapy is used for radiosensitization (with concurrent external beam radiation therapy) and palliation (recurrent and/or metastatic disease or inoperable). Induction chemotherapy (IC) is one of the most important changes in the management of patients with LASCC of the head and neck over the last 30 years, in particular with the introduction of taxanes.

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In contrast, endpoint evaluation [overall survival (OS), disease-free survival, locoregional control or recurrence, and distant metastases] needs to include preserved organ function and patient quality of life. It is necessary to precisely identify the position of IC (and its intensification), within the armamentarium of other strategies aiming at better locoregional treatment [normofractioned radiotherapy (RT), accelerated or hyperfractionated, addition of concurrent chemotherapy, or targeted therapy] or adjuvant treatment. This review summarizes the rationale, these data, and perspectives on the IC strategy.

Induction rationale and evolution before taxanes

The concept of IC developed after the identification of platinum chemotherapy efficacy in head and neck cancers [13] and after the addition of 5-fluorouracil (5-FU) paired to cisplatin [14,15].

The use of IC in SCC of the head and neck (SCCHN) has several theoretical advantages

(1) It induces tumor shrinkage, which allows more effective and less toxic local therapy, whether RT or surgery.
(2) It potentially reduces distant metastatic disease because of systemic exposure.
(3) It optimizes the delivery of chemotherapeutic drugs through a vasculature that has not been disrupted by surgery or radiation.
(4) It permits assessment of tumor responsiveness and alters subsequent therapy accordingly.
(5) It induces tumor cell death independently of the effects of RT with different toxicity profiles.

Numerous studies have investigated the efficacy of this concept.

In the Paccagnella randomized phase III trial, the investigators compared the cisplatin and 5-FU (PF) IC regimen before locoregional therapy versus locoregional therapy alone for operable and inoperable 112 patients with stage III–IV disease [16,17]. The objective tumor response rate was 80% with no significant difference in OS between the two arms and a trend in terms of survival advantage for patients with inoperable disease.

In another randomized study in Italy conducted for patients with resectable oral cavity stage II–IV squamous cell cancer [18], three PF cycles followed by surgery were compared with primary surgery. RT was allowed for patients with high risk of recurrence. OS between the two groups was comparable as 55% at 5 years; however, mandible resection was less performed in the IC arm related to tumor response, (52 vs. 31%).

The GETTEC group carried out a randomized study [19] for patients with oropharynx stage II–IV squamous cell cancer compared with PF IC (three cycles) followed by locoregional treatment versus locoregional treatment alone (RT with or without surgery). The response rate to PF chemotherapy was 56% and the median OS was, respectively, 5.1 and 3.3 years in the induction and the control arms.

This new concept of IC was in particular tested for organ preservation focusing on larynx and hypopharynx cancers. Until the early 1990s, the standard treatment for locally advanced larynx and hypopharynx SCC was total laryngectomy followed by conventional RT with a negative impact on the patient's quality of life because of permanent tracheotomy, loss of a natural voice, social isolation, loss of employment, and depression. The main causes of treatment failure were not only locoregional recurrences, but also distant metastases (40–60%) [20,21].

Induction chemotherapy with cisplatin and 5-FU followed by RT in patients who had responded to IC at the primary site was considered as an alternative to total laryngectomy after the publication of two large experimental randomized trials. When comparing IC with total laryngectomy the patients achieved good larynx preservation rates (40–64%) without compromising disease control and survival rates [21,22].

The Veterans Administration Laryngeal Study Group [22] trial, in 1991, randomized 332 patients with earlier untreated and advanced (stage III or IV) laryngeal squamous carcinoma to compare the results of IC (PF) followed by definitive RT with those of conventional laryngectomy and postoperative radiation. Larynx preservation was achieved in two-thirds of patients who survived in the PF IC arm.

The European Organization for Research and Treatment of Cancer [21] conducted a similar study for 194 patients with LASCC of the pyriform sinus, requiring complete response at the primary site to proceed with radiation. A similar control rate was obtained.

At this stage of the evolution of concepts based on IC, evidence-based medicine validated another approach: concurrent chemoradiotherapy in locally advanced diseases particularly for head and neck cancer [20,23–30]. These results were confirmed by the large *Meta-Analyses of Chemotherapy in Head and Neck Cancer* published in 2000 [31] and recently updated [32]. In the original publication, 63 randomized phase III trials were conducted between 1965 and 1993; 10 741 patients were analyzed. Chemotherapy delivered as a neoadjuvant, concurrent, or adjuvant treatment was found to confer an absolute OS benefit of 4% at 5 years. The greatest benefit was observed in the concurrent chemoradiotherapy group (8% at 5 years). Concurrent chemoradiotherapy had the highest impact on survival. Induction chemotherapy was associated with a 2% absolute benefit in OS at 5 years, but there was no statistically significant difference. However, when the analysis was limited to PF IC regimens, there was a significant benefit for survival ($P = 0.01$; hazard ratio 0.88, 95% confidence interval 0.79–0.97).

The 2009 publication of *Meta-Analyses of Chemotherapy in Head and Neck Cancer* added randomized trials conducted between 1994 and 2000 [32]. Twenty-four new trials (mostly concomitant chemotherapy) were included with a total of 87 trials and 16 485 patients. The hazard ratio of death was 0.88 ($P < 0.0001$) with an absolute benefit for chemotherapy of 4.5% at 5 years, and a significant interaction ($P < 0.0001$) between chemotherapy timing (adjuvant, induction, or concomitant) and treatment. Both direct (six trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy compared with IC. For the 50 concomitant trials, the hazard ratio was 0.81 ($P < 0.0001$) and the absolute benefit was 6.5% at 5 years. This benefit was confirmed but was less clear than in 2000. It is important to keep in mind that IC used in this analysis did not include taxanes regime, and therefore the benefit from IC with taxanes may be more pronounced that it seems here.

A direct comparison was conducted during the Radiation Therapy Oncology Group 91-11 trial that compared three treatments: IC with PF followed by RT, concurrent chemoradiation with cisplatin, and RT alone [33]. This trial suggested the superiority of the concomitant regimen in terms of laryngeal preservation and locoregional control; both chemotherapy arms tended toward better survival. At 2 years, the proportion of patients who had an intact larynx after RT with concurrent cisplatin therapy (88%) differed statistically and significantly from the proportions in the groups that were given IC followed by RT (75%, $P = 0.005$) or RT alone (70%, $P < 0.001$). However, severe toxicity was more frequent in the concurrent schedule: the 5-year probability of survival with a functional larynx was 45% in the concurrent chemoradiotherapy group and 43% in the IC group, and no differences in OS were observed [34]. Compared with a concurrent chemoradiotherapy schedule, IC for head and neck cancer was less toxic for patients, particularly those with larynx cancer (odds ratio, 4.17; $P = 0.0041$), who more frequently develop severe late toxicities after concurrent chemoradiation [35]. Preserving the organ function is more important than preserving the organ itself and this principle is now established especially for larynx cancer [36].

Taxanes

Taxanes constitute the newest and one of the most active classes of cytotoxic agents against SCCHN. Recent data from phase I, II, and III trials suggest that taxanes (docetaxel and paclitaxel) may add to the efficacy of conventional chemotherapy (cisplatin based or others) [37–55] and may increase the OS rate [56,57].

Paclitaxel was tested in a phase II trial [38] as a single agent in 34 patients with recurrent, metastatic, or locally advanced incurable SCCHN. Response was observed in 40% of eligible patients, with four complete and eight partial responses. In a combination with carboplatin or cisplatin, 5-FU was tested in other studies and it showed better efficacy than in the absence of paclitaxel. These results confirmed that paclitaxel is an active agent for these cancers.

In a phase II trial, Hitt *et al.* [39] evaluated the efficacy and toxicity of a combination of paclitaxel, cisplatin, and 5-FU (PPF) in 70 patients with locally advanced head and neck cancer. Induction treatment consisted of a maximum of three outpatient courses of paclitaxel (175 mg/m^2) on day 1, cisplatin (100 mg/m^2) on day 2, and 5-FU (500–750 mg/m^2/day; reduction for toxicities after 14 treated patients) on days 2–6, followed by RT and/or surgery. The overall response rate was 88%, including 59% complete responses and 29% partial responses. The estimated 5-year time to disease progression and OS rates were, respectively, 56 and 44%.

In 2005 [41], the same team enrolled 382 patients in a phase III study that compared three PPF with three PF arms [cisplatin (100 mg/m^2) on day 1 and 5-FU (1000 mg/m^2/day) on days 1–5]. In the case of more than 80% primary tumor response, patients received definitive RT at 70 Gy in combination with cisplatin (100 mg/m^2) on days 1, 22, and 43. The complete response rate in the PPF arm was 33% compared with 14% for the control arm ($P < 0.001$). In the control arm, 44% received concomitant chemoradiotherapy versus 63% in the PPF arm. OS was not significantly different between the two arms (37 vs. 43 months) but was in favor of the PPF regimen if the unresectable disease remained (26 vs. 36 months, $P = 0.04$).

The introduction of docetaxel in combination with PF (TPF) improved the overall tumor response rate and has led to renewed interest in IC. The TPF regimen with a dose adaptation of PF was reported in phase I, II, and III trials with an increased response rate [43–57]. Response rates have ranged from 50 to 100% with little opportunity for improvement.

Phase I–II trials showed [48,52] the efficacy of adding docetaxel to PF with good tolerance. In phase I–II trials, Posner *et al.* determined the maximum-tolerated dose of docetaxel in combination with cisplatin and 5-FU for 43 patients treated for SCCHN. All patients received docetaxel (75 mg/m^2) on day 1; cisplatin at 75 (level I) or 100 (level II) mg/m^2 on day 1; and a continuous FU infusion at 1000 mg/m^2/day on days 1–4. The investigators concluded that TPF can be delivered safely with a cisplatin dose of 100 mg/m^2 with a high response rate but with some toxicity.

This activity has stimulated the conduct of phase III trials that have directly compared IC using TPF against PF. Thus, these studies evaluated the addition of a third chemotherapy agent. Although cisplatin and PF alone are not considered a standard therapy option outside of the larynx preservation setting, the meta-analysis of

chemotherapy supports that its use as a control arm should at least mimic that of standard therapy, if not exceed its effects on survival.

Three published randomized phase III trials [55–57] using the TPF regimen followed by RT alone (GORTEC 2000–2001 and TAX 323) or with carboplatin (TAX 324) confirmed the superiority of TPF compared with the PF regimen for response rates and for TAX trials on OS and progression-free interval (PFS) [56,57].

In the TAX 323 trial [56], patients with unresectable stage III or stage IV disease and no distant metastases were randomly assigned to the TPF group (docetaxel and cisplatin both 75 mg/m^2 on day 1, and 5-FU 750 mg/m^2/day on days 1–5) or the PF group (cisplatin 100 mg/m^2 on day 1 followed by 5-FU 1000 mg/m^2/day on days 1–5). Four cycles were planned every 3 weeks. Patients without progression of disease received single-modality RT up to 70 Gy or accelerated or hyperfractionated regimens (total maximum dose of 70 and 74 Gy, respectively). A total of 358 patients underwent randomization, with, respectively, 177 and 181 patients assigned to the TPF and PF arms. The overall response rate after IC was 68 versus 54% in favor of TPF ($P = 0.006$). The median PFS was 11.0 months in the TPF group and 8.2 months in the PF group ($P = 0.007$). The distant disease was the first site of failure in 13% of TPF patients and 10% of PF patients. The median OS was 18.8 months in the TPF group compared with 14.5 months in the PF group.

In the TAX 324 trial [57], patients with stage III or IV disease with no distant metastases and tumors considered to be unresectable or were candidates for organ preservation were randomly assigned to the TPF group (docetaxel 75 mg/m^2 on day 1, cisplatin 100 mg/m^2 on day 1, and 5-FU 100 mg/m^2/day on days 1–4) or the PF group (cisplatin 100 mg/m^2 on day 1 followed by 5-FU 1000 mg/m^2/day on days 1–5). Three cycles were planned every 3 weeks. All patients received RT between 70 and 74 Gy and weekly carboplatin at an area under the curve of 1.5. A total of 501 patients were analyzed. The overall response rate after IC was 72 versus 64% in favor of TPF ($P = 0.07$). The median OS was 71 months (95% confidence interval = 49–not reached) in the TPF group and 30 months in the PF group (95% confidence interval = 21–52; $P = 0.006$). The locoregional control rate was higher in the TPF group than in the PF group. The distant disease failure was 5% of TPF patients and 9% of PF patients.

More recently, the final results of GORTEC 2000–2001 [55], which was specifically designed for larynx preservation, randomized 213 patients with larynx and hypopharynx cancer that required total laryngectomy. Eligible patients received three cycles of TPF (docetaxel and cisplatin both 75 mg/m^2 on day 1 and 5-FU 750 mg/m^2/day on days 1–5) or standard PF (cisplatin 100 mg/m^2 on day 1 followed by 5FU 1000 mg/m^2/day on days 1–5). Patients who had responded to chemotherapy received RT with or without additional chemotherapy. Patients who did not respond to chemotherapy underwent total laryngectomy followed by RT with or without additional chemotherapy. Baseline patient and tumor characteristics were well balanced between the TPF ($n = 110$) and PF ($n = 103$) groups. The overall response was 80% in the TPF group versus 59.2% in the PF group (difference = 20.8%; $P = 0.002$). With a median follow-up of 36 months, the 3-year actuarial larynx preservation rate was 70.3% with TPF versus 57.5% with PF (difference = 12.8%; $P = 0.03$). TPF improved larynx preservation with better tolerance but without gain in survival.

These three trials also reported better compliance and quality of life with the TPF regimen than the PF regimen. Febrile neutropenia during chemotherapy occurred, respectively, in 5.2, 12, and 10.9% of TPF patients in TAX 323, TAX 324, and GORTEC 2000–2001.

During the 2009 American Society of Clinical Oncology Annual Meeting, Hitt *et al.* [42] presented, in an oral communication, the results of a randomized phase III study. A total of 439 patients with stage III–IV (M0) HNSCC were randomized to receive concomitant chemoradiotherapy with cisplatin (100 mg/m^2/day on days 1, 22, and 43); induction standard PF was followed by the same concomitant chemoradiotherapy or TPF followed by concomitant chemoradiotherapy. The primary endpoint was time to treatment failure. The investigators reported a significant improvement in the time to treatment failure for patients treated with IC versus patients treated with primary chemoradiation (12.5 vs. 5 months, $P < 0.001$) but they pooled the two arms without complete analysis. However, as a large number of patients had been excluded from this first analysis, no firm conclusion could be made and further detailed information is warranted.

These studies have shown that TPF induction is superior to PF induction. The increase in survival has established TPF as the standard of care when IC-based strategy is selected.

Some clinical trials showed that its incidence of distant metastases has seemed to increase and that the pattern of treatment failure and the main cause of death may be shifting from locoregional control to metastatic disease [58,59].

These circumstances have provided the impetus to develop IC regimens to be used in conjunction with concurrent chemoradiation with the intent of further improving the OS. This treatment strategy has been referred to as sequential chemoradiation. A fundamental principle of these efforts is that the value of IC should be determined within the context of optimized locoregional therapy.

The role of epidermal growth factor receptor inhibitor

Another recent innovation was the development of the monoclonal antibody cetuximab, which targets the epidermal growth factor receptor (EGFR). Head and neck cancer overexpresses EGFR associated with a poor outcome [60,61]. Cetuximab or erbitux is an IgG1 monoclonal antibody that inhibits ligand binding to the EGFR [62]. It also enhances the activity of cisplatin [63]. Its impact was validated in the EXTREME trial that tested the efficacy of cetuximab and platinum-based chemotherapy as a first-line treatment in patients with recurrent or metastatic SCCHN [64]. A total of 442 patients were randomized to receive either cisplatin or carboplatin and 5-FU every 3 weeks or the same chemotherapy and cetuximab (400 mg/m^2 the first time and then 250 mg/m^2 per week). For the first time in 30 years, adding cetuximab to platinum-based chemotherapy with FU significantly prolonged the median OS from 7.4 to 10.1 months ($P = 0.04$). Moreover, the investigators reported prolongation of the median PFS time from 3.3 to 5.6 months ($P < 0.001$) and increased response rate from 20 to 36% ($P < 0.001$). Toxicities were mostly skin and infusion-related reactions.

Cetuximab was also tested in combination with RT compared with RT alone [65,66] for patients with locoregionally advanced head and neck cancer. They were randomly assigned to treatment with RT alone (213 patients) or RT and weekly cetuximab (211 patients: initial dose of 400 and then 250 mg/m^2 weekly during RT). Three RT-fractionation regimens were allowed with conventional 70 Gy delivered in 35 fractions of 2 Gy, a twice-daily schedule in 60–64 fractions to a total dose of 72–76.8 Gy, or a concomitant boost to total radiation dose at 72 Gy in 42 fractions. Cetuximab improved locoregional control and OS rates without increasing acute mucosal reaction. The reported median duration of locoregional control was 24.4 months for patients who were treated with cetuximab and RT and 14.9 months for those treated with RT alone ($P = 0.005$). The median duration of OS was 49 months for patients treated with combined therapy and 29.3 months for those treated with RT alone ($P = 0.03$). Cetuximab and RT statistically prolonged the PFS ($P = 0.006$). Incidence of grade 3 or greater toxic effects, including mucositis, did not statistically differ between the two groups with a majority of rash. An update was recently published reporting a 5-year OS of 45.6% in the cetuximab-and-RT group and 36.4% in the RT-alone group. In addition, for the patients treated with cetuximab, OS was significantly improved in those who experienced an acne-form rash of at least grade 2 severity compared with patients with no rash or grade 1 rash (hazard ratio 0.49, 0.34–0.72; $P = 0.002$).

The next step was to test cetuximab during IC.

Over the last two American Society of Clinical Oncology annual meetings, the use of this combination was only reported in a few abstracts.

In 2009, Mesia *et al.* [67] proposed a phase II trial including cetuximab with TPF (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, 5-FU 750 mg/m^2 on days 1–5) for four cycles with prophylactic antibiotics and granulocyte colony-stimulating factor support followed by accelerated RT with a concomitant boost (69.9 Gy) and cetuximab (250 mg/m^2 weekly) in 50 patients with unresectable stage IV SCCHN. Objective response was obtained in 78% of cases but serious grade 3/4 adverse events were described, particularly neutropenia (24%) and neutropenic fever (20%).

Another phase II trial incorporated [68] cetuximab into induction therapy and subsequent concomitant chemoradiotherapy of HNC. Patients with previously untreated stage III or IVA–B HNC were treated with TPE (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and cetuximab 250 mg/m^2 on days 1, 8, and 15 after an initial dose of 400 mg/m^2 on cycle 1, day 1), and this was repeated every 21 days for three cycles, followed by RT up to 70 Gy (2 Gy/day) with concurrent cisplatin 30 mg/m^2 and cetuximab 250 mg/m^2 weekly, and maintenance cetuximab for 6 months. A total of 39 patients were enrolled, with majority of who had IV disease. With a median follow-up of 36 months, 2-year and 3-year PFS was 70 and 67%, respectively; 2-year and 3-year OS was 77%. HPV positivity was found in 67% of 27 evaluable tumor specimens, and did not alter PFS or OS.

DeLOS II [69] is a randomized phase II trial comparing four TPF IC with or without cetuximab for patients with only laryngectomy operable carcinoma of the larynx/hypopharynx, followed by RT and cetuximab in case of objective response. Total enrollment in January 2010 was 78 patients. On account of five toxic deaths among the first 62 patients, 5-FU was omitted from the IC. In this trial, TPF with cetuximab is an effective schedule but has an unacceptable toxicity level, and using TP with cetuximab is feasible.

The E2303 trial [70] evaluated cetuximab with induction CT (paclitaxel 90 mg/m^2 and carboplatin area under the concentration curve = 2/week × 6) followed, in the case of response, by RT and cetuximab (and chemotherapy) in patients with resectable stage III–IV SCCHN. Of 74 enrolled patients, 70 had induction and 68 had concurrent chemoradiotherapy. Ninety-one percent of the 63 eligible patients had complete histopathological response during re-biopsy. Data on toxicities are not shown.

Overall, we can conclude that TP (± F) with or without cetuximab may be an alternative for patients for whom induction chemotherapy followed by radiation is indicated, but toxicities can be limiting and need to be tested in phase III trials.

Conclusion

TPF has acquired an indisputable place in chemotherapy induction on the basis of a group of convergent

arguments: the toxicity is acceptable; in comparison with the PF regimen, TPF significantly improved locoregional control in the three published randomized trials; and there is improved OS and disease-free survival in the two TAX trials. TPF achieved objective responses in approximately two-thirds of patients.

However, numerous issues remain unresolved:

(1) What is the optimal number of cycles of IC (three, four, more?)
(2) How and when should response to treatment be assessed? Imaging and endoscopy play an essential role. Several methods of image measurement and response to treatment evaluation exist (World Health Organization, Response Evaluation Criteria In Solid Tumors). In addition to the contribution of PET-computed tomography or functional MRI, the move toward a volume assessment before, during, and after treatment is another method of future evaluation. Delaying this assessment until the end of the third cycle may cause a delay in initiating the local therapy. Thus, a response assessment after the second cycle could be useful to discriminate good and poor responders.
(3) How can TPF be improve or optimized? The addition of an anti-EGFR-targeted therapy (cetuximab) to TPF chemotherapy (TPF-E) or by removing the 5-FU (TPE) seems to be interesting. Some toxicity are found during phase I–II trials but.
(4) How should the TPF induction protocols in so-called sequential chemoradiotherapy be integrated? This question relates to the contribution of this strategy compared with chemoradiation and the type of locoregional treatment (conventional or modified RT alone or combined with chemotherapy or molecular-targeted therapy).
(5) What are the indications for IC: organ preservation, nonresectable tumors, high metastatic risk, bulky primary or node diseases?

We need to compare frontline IC (better schedule?) with concurrent chemoradiotherapy in patients divided into specific groups (organ preservation, unresectable disease, oral cavity vs. oropharynx versus hypo-pharyngolaryngeal cancers).

To clarify the contribution of induction chemotherapy, ongoing studies compare sequential approach versus immediately concurrent chemoradiotherapy. DeCIDE and PARADIGM trials will be available soon. The preliminary toxicity data of the PARADIGM trial were presented during the 2010 annual American Society of Clinical Oncology meeting [71]. This is a multicenter phase III study comparing three cycles of TPF followed by RT with either weekly carboplatin or docetaxel with concurrent cisplatin RT in patients with locally advanced stage III or IV disease. A total of 145 patients were enrolled with a majority of oropharynx. The preliminary report does not show any unusual patterns of toxicities in either arm. Analysis of late toxicities and study outcomes is under way.

A new meta-analysis including recent data on the TPF regimen is required to evaluate the impact on survival and to be compared with chemoradiation.

On account of the potential long-lasting toxicities of these treatments, particularly with regard to swallowing, functional studies need to be carried out to assess the effects of these newer treatments.

Future trials should be designed to compare the concomitant schedule with the induction approach using TPF. Emphasis should be put on the functional results and quality of life associated with these approaches.

Using cetuximab in association with induction chemotherapy (TP ± F) seems to be interesting with some toxicity reported in previous phase I–II study; however, its impact must be confirmed by phase III studies.

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