CLINICAL INVESTIGATION

Clinical trial design in advanced head and neck cancer: from past experiences to future perspectives

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Head and neck squamous cell carcinoma (HNSCC) is usually diagnosed in advanced stages and it is more prevalent in the developing world, as a consequence of heavy exposure to smoking, alcohol drinking and human papillomavirus infection. Current multidisciplinary treatment includes surgery and/or radiation therapy in early stages, cisplatin-based concurrent chemoradiation in locally advanced disease and chemotherapy in patients with relapsed/metastatic HNSCC. Molecular targeted therapies, especially directed to the EGFR, have also been incorporated in the current therapeutic armamentarium. However, the low long-term overall survival and the high rate of acute and late toxicities still remain problematic. In this article, the authors aim to briefly review and discuss some aspects to be better addressed in future clinical studies in advanced HNSCC.

Keywords: chemotherapy • clinical trials • EGFR • head and neck cancer • human papillomavirus • larynx preservation • molecular targeted therapy • squamous cell carcinoma

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The term head and neck cancer usually refers to those malignant tumors arising on the upper aerodigestive tract, with the primary site in the oral cavity, pharynx and larynx, with squamous cell carcinoma (SCC) being by far the most common histologic type. Usually, these tumors are grouped as a single entity in most clinical studies, as they share the most important risk factors: heavy exposure to smoking and alcohol. As a group, they represent approximately 645,000 new cases and more than 350,000 deaths per year worldwide, with >75% of all patients diagnosed with stage III–IV disease [1,2]. They figure among the top cancer-related causes of death in developing countries. Oral cancer, for instance, is the most common cancer type and the most frequent cancer-related cause of death in India [3]. In addition, a rising trend in oral-cancer mortality has been detected in some European countries, despite being largely preventable and easily diagnosed [4].

In general, as a group these cancers present an unfavorable prognosis, with a long-term disease-free survival rate of 50%. When diagnosed in early stages (I–II), the 5-year overall survival rate is approximately 80%, but these rates are considerably lower (10–50%) in those patients diagnosed in locally advanced stages (III–IV). Multimodality treatment must be considered in all patients, with surgery and radiation therapy (RT) being the main modalities to be considered for early-stage diseases; systemic therapies are added in those patients with locally advanced disease. Unfortunately, those patients with metastatic head and neck SCC (HNSCC) are treated with palliative intent.

This article aims to briefly review some aspects of clinical trial design, including current end points and stratification aspects currently used in large Phase III studies in HNSCC. Potentially useful aspects to be considered in future studies in this population are also presented.

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Locally advanced HNSCC: locoregional therapy

One important aspect to be discussed first, is the definition of locally advanced HNSCC. Patients diagnosed with locally advanced HNSCC may present with resectable disease and the treatment decision favoring radical surgery must always consider important aspects, such as anatomic and functional sequelae, comorbidities (e.g., anemia, malnutrition and pulmonary diseases), quality of life, human and material resources and team expertise, among others. Consequently, those studies including locally advanced HNSCC patients considered as 'unresectable' must clearly state what the criteria considered for eligibility are. Circular involvement of carotid artery, gross involvement of the base of skull and/or prevertebral fascia are the classical features characterizing unresectability.

Cisplatin (P)-based concurrent chemoradiation is the treatment of choice for those HNSCC patients diagnosed with locally advanced disease who are not candidates for surgery with curative intent, according to randomized Phase III trials and the MACH-NC meta-analysis [5–16]. The MACH-NC individual patient data meta-analysis, in the last update published in 2009, analyzed 16,485 patients included in 87 randomized studies for nonmetastatic HNSCC [16]. Overall, the hazard ratio (HR) for death was 0.88 in favor of adding chemotherapy to locoregional therapies, with an absolute benefit of 4.5% at 5 years. The absolute overall survival benefit associated with the concurrent administration of chemotherapy was 6.5% at 5 years (HR: 0.81). It is important to mention that this benefit is restricted to patients with Eastern Cooperative Oncology Group performance status 0–1, aged <70 years of age [16].

Randomized studies addressing the value of concurrent chemoradiation do support platin-enhanced regimens [5–15]. Increased locoregional control and overall survival gains were observed in the concurrent chemoradiation arms, at the price of higher rates of grade 3–4 acute and late toxicity, particularly in terms of mucositis, dermatitis, dysphagia, bone marrow and nephrotoxic effects. Based on the best available data, P 100 mg/m^2 administered intravenously every 3 weeks is considered as the standard regimen of concurrent chemoradiation and once-weekly regimens [17] or even daily administration [10] should be limited to clinical studies.

Altered fractionation schemes of RT are considered as superior to conventionally delivered RT, according to randomized studies [18,19] and a meta-analysis [20], with overall survival gains. The benefit of adding concurrent chemotherapy in hyperfractionated RT regimens has already been demonstrated [9–13]. Unacceptable treatment-related toxicity did limit the delivery and final outcomes in studies that evaluated concurrent chemotherapy and intensified accelerated RT [14,21].

When exploring radiation-enhancing therapies, some aspects must be considered in clinical trial designs. Anemia is an important prognostic factor in this population and must be considered as a stratification factor [6,22]. How to reduce toxicity and the incorporation of biomarkers to better predict treatment response and outcomes are unmet requirements. Trials specifically designed for those HNSCC patients presenting with locally advanced disease and Eastern Cooperative Oncology Group performance status 2 must be a priority.

Oropharyngeal SCC & human papillomavirus-related tumors

Oropharyngeal SCC must be considered as a unique entity. In addition to smoking and alcohol habits, human papillomavirus (HPV) has emerged as another risk factor for developing oropharyngeal SCC [23–27]. HPV-positive oropharyngeal SCC presents distinct epidemiological, morphological and molecular characteristics, including lower p53 mutation rate, higher frequency of basaloid tumors, higher expression of p16 and a better response to chemotherapy and RT. These patients diagnosed with HPV-positive oropharyngeal SCC also had better overall survival outcomes in comparison with those with HPV-negative tumors [25,26].

Consequently, to better stratify patients in randomized studies on locally advanced oropharyngeal SCC, HPV status must be determined prior to randomization. Usually, those with oropharyngeal SCC are considered as HPV-positive when presenting positive p16 expression by immunohistochemistry and/or positive *in situ* hybridization for (high-risk) HPV (e.g., HPV-16 and -18). The E1308 study is a Phase II study evaluating induction chemotherapy (IC; paclitaxel, carboplatin and cetuximab [C]) followed by RT (intensity-modulated RT) and C in resectable stage III–IV HPV-positive oropharyngeal SCC [101]. There is a hope that HPV-positive oropharyngeal SCC patients could be treated with less toxic therapies, but this hypothesis must be tested in prospective studies.

EGFR-targeting agents

EGFR is usually overexpressed in HNSCC, conferring worse prognosis, higher relapse rate after locoregional treatment and resistance to chemotherapy and RT [28]. Many EGFR-targeting agents, including monoclonal antibodies and EGFR-tyrosine kinase inhibitors (TKIs) are in different phases of clinical development.

Cetuximab is currently available worldwide for the treatment of locally advanced HNSCC in combination with RT [29] and also for patients with relapsed/metastatic HNSCC, in association with platinum-based chemotherapy [30].

In contrast to colorectal cancer and non-small-cell lung cancer, no biomarker has been described to better identify those HNSCC patients who may benefit or not from EGFR-targeting agents. The acneiform rash (grade 2–3), when present as an adverse effect after C administration, is associated with better survival outcomes [29]. A very interesting study investigated zalutumumab, a human IgG1 monoclonal antibody targeting EGFR, after failure of platinum-based chemotherapy in recurrent/metastatic HNSCC patients. In this trial, zalutumumab was administered weekly by individual dose titration on the basis of skin rash, versus best supportive care (including methotrexate) in the control arm. Better progression-free survival was observed in those patients treated with zalutumumab (HR: 0.63; p = 0.0012), but no difference in terms of overall survival (the primary end point) was observed [31]. The anti-EGFR monoclonal antibody nimotuzumab is under evaluation in HNSCC and presents very low incidence of skin rash [32].

As EGFR-activating mutations are virtually absent in HNSCC, the number of *EGFR*-gene copies was investigated as a predictive biomarker for the efficacy of C in those patients enrolled in the EXTREME study, but high-level amplification of the gene occurred in only a small fraction of tumors (11%) and no association of *EGFR*-gene copy number with overall survival, progression-free survival or best overall response was found [33]. A serum proteomic profile is under validation as a tool to evaluate EGFR-pathway dependence in HNSCC patients [34].

Surprisingly, among patients enrolled in the SPECTRUM study, in which panitumumab in combination with 5-fluoruracil (F) and P was compared with chemotherapy alone as first-line treatment for relapsed/metastatic HNSCC, an overall survival gain was observed in the HPV-negative subset: 11.8 months in the panitumumab-containing arm versus 8.6 months in the chemotherapy-alone arm (HR: 0.73; p = 0.02). In contrast, in the HPV-positive subset, the addition of panitumumab was not associated with a survival benefit (10.9 vs 12.1 months, respectively). The test for interaction, however, was not significant (p = 0.332), possibly due to small numbers of patients in the HPV-negative group [35]. This reinforces the importance of adequately stratifying patients according to HPV status. In addition, the negative survival results of the Phase III trial RTOG 0522, evaluating the addition of C to concurrent P-based chemoradiation in locally advanced HNSCC, can be partially explained by the high number of patients presenting with oropharynx as the primary site (and possibly with a high frequency of HPV-positive tumors) [36].

TKIs, such as gefitinib, erlotinib and afatinib, have also been evaluated in advanced HNSCC. Gefitinib was compared with methotrexate in the IMEX study in patients with recurrent and/or metastatic HNSCC and neither gefitinib 250 nor 500 mg/day improved overall survival when compared with intravenous methotrexat, and more hemorrhagic events were observed in the gefitinib-containing arms [37]. Erlotinib was studied in combination with bevacizumab in a Phase I/II study, in which complete responses were seen in patients with recurrent/metastatic HNSCC presenting with expression of putative targets in tumor samples [38]. Recent data on afatinib are discussed below (see section on 'Relapsed &/or metastatic HNSCC').

Despite the lack of a predictive marker of response, C was successfully incorporated in the treatment of HNSCC. Future studies must explore biological markers to allow better patient selection, as well as how to overcome the resistance to these agents, maybe mediated through signaling transduction pathways activated by IGF-I receptor, PI3K and c-Met.

Induction chemotherapy

Sequential therapy, or IC followed by (chemo-)RT is a treatment option in HNSCC patients with locally advanced disease. The response rate to IC theoretically allows a symptomatic relief and may not compromise the RT delivery. The triplet combination of docetaxel (T), P and F has been used as IC after two randomized studies published in 2007 showned its superiority over PF, when followed by (chemo-)radiation [39,40]. In fact, if TPF-based IC is more effective than upfront concurrent P-based chemoradiation remains to be proven.

The Phase II results of the Italian study in 101 patients diagnosed with locally advanced stage III–IV HNSCC showed that TPF did not compromise chemoradiation delivery and the complete-response rate reached 50% 6–8 weeks after the end of treatment, in comparison with 21% after chemoradiation alone. The 1-year survival rate was 86 versus 78%, respectively. The Phase III part of the study is ongoing [41]. In a Spanish study, 439 patients with locally advanced HNSCC were randomly assigned to receive concurrent chemoradiation or the same treatment after P plus F with or without T. Time-to-treatment failure increased from 5 to 12.5 months in those patients treated with IC. Better locoregional control was observed in 61.5% of patients treated with the sequential strategy versus 44.5% of those patients treated with concurrent chemoradiation alone (p = 0.002) [42]. To add C or EGFR-TKIs to TPF as IC in

order to improve the response rate has also been studied. The Phase I data of C-TPF as IC in locally advanced HNSCC patients suggest that C-TPF is possibly a safe combination, when reducing F to 850 mg/m^2 daily in order to prevent serious gastrointestinal toxicity [43].

In terms of biomarkers, to select those patients who are the best candidates for TPF-based IC is also a relevant issue to be explored. Those patients whose tumors present with lower expression of β-tubulin-II seem to be more likely to benefit from TPF [44]. Among those patients with oropharyngeal SCC, again those HPV-positive patients present with better outcomes and can be considered for less-intensive protocols [24]. Cost–effectiveness of IC in different countries must also be better explored [45].

Larynx preservation

After the VA and EORTC studies [46,47], larynx preservation can be considered as a treatment option for those patients diagnosed with laryngeal SCC. In these studies, those patients whose tumors were proven to be responsive to F and P could be safely treated with RT alone with no impact on overall survival, in comparison with total laryngectomy followed by adjuvant RT. Upfront P-based concurrent chemoradiation was considered initially as the most successful strategy in terms of laryngectomy-free survival, according to the first results of the Intergroup RTOG 91–11 trial [48], in which 515 patients with resectable stage III–IV glottic or supraglottic laryngeal SCC were included. The last update of the RTOG 91–11 trial, with a median follow-up for surviving patients of 6.9 years, indicated a best locoregional control in the concurrent chemoradiation arm, but no difference in terms of laryngectomy-free survival between the upfront chemoradiation arm and the IC followed by RT arm [49].

More recently, IC based on a three-drug regimen (TPF) was compared with the classic PF induction regimen in the GORTEC trial and it was shown that the 3-year actuarial larynx-preservation rate was 70.3% with TPF versus 57.5% with PF ($p = 0.03$) [50]. Future trials on larynx preservation are being designed to compare upfront chemoradiation, TPF followed by (chemo)radiation and also to explore the role of anti-EGFR agents in this setting. In the TREMPLIN study, those patients who responded to induction TPF (three cycles), were randomized to receive either P-based chemoradiation, or RT and concurrent C. There was no difference in the larynx-preservation rate among the two arms (92 vs 96%, respectively), but the C-containing arm was better tolerated [51].

It is important to mention that recent recommendations were reported regarding the end points to be adopted in designing larynx-preservation trials, minimum needed assessments, the best candidates to this treatment and the use of biomarkers, as shown in **Box 1** [52]. To strictly follow these recommendations is of utmost importance, due to recent data indicating a rise in laryngeal-cancer mortality in the USA, maybe related to an overuse of larynx-preservation chemoradiation protocols in advanced cases, otherwise better treated with total laryngectomy [53–55].

Adjuvant treatment

High-risk clinical–pathological factors, as positive margins and extracapsular spread of nodal disease, are used in the current clinical practice to identify those patients who need to be treated with P-based chemoradiation in the adjuvant setting, following surgery with curative intent [56,57]. In our opinion, we need to incorporate molecular markers to help us to better select these patients, especially considering the high-toxicity rate of P-based chemoradiation in the adjuvant setting. One option would be to study those proteins involved in DNA repair, such as ERCC1, a major component of the nucleotide-excision repair machinery [58].

Relapsed &/or metastatic HNSCC

Relapsed/metastatic HNSCC remains a challenge in the daily clinical practice. These patients are considered incurable and usually present with low performance status, a high tumor burden and with a very symptomatic disease. As first-line treatment, the combination of F, platinum and C is considered as the best therapeutic choice, based on the results of the EXTREME study [30].

More recently, in platinum-refractory patients, afatinib (BIBW2992) was compared with C in this setting, in a Phase II study, with crossover in progressive patients. Response rate (before crossover) was 18 versus 8%, favoring afatinib [59]. Afatinib is being compared with methotrexate in metastatic/advanced, platinum-refractory HNSCC patients [102].

Other classic cytotoxic agents have also been investigated in this setting, focusing on platinum-refractory patients. In a small Phase II study, the combination of gemcitabine and doxorubicin presented a response rate of 24% in 17 relapsed/metastatic HNSCC patients, all platinum refractory [60]. More interestingly, the investigators concluded that C18-ceramide elevation in serum may be a marker of response in this setting.

In summary, despite the fact that some advances in platinum-sensitive patients were reported, the development of active agents for platinum-refractory disease is urgently needed.

Box 1. Key issues and recommendations for studies on larynx preservation.

Patient selection
- Laryngeal or hypopharyngeal squamous cell carcinoma
- T2–T3
- Not considered for partial laryngectomy
- No laryngeal dysfunction (no tracheotomy, recent pneumonia or tumor-related dysphagia requiring feeding tube)
- <70 years of age

Stratification factors
- Supraglottis/glottis or epilarynx/hypopharynx
- N0–1 or N2–3
- Geographic region

Baseline assessment
- CT or MRI, endoscopic evaluation and barium esophagram

On-treatment assessments
- Response and restoration of vocal-cord mobility (in case of induction chemotherapy, after two cycles; after 2 and 3 months after the last day of radiation therapy)

Salvage surgery
- Total laryngectomy, but partial laryngectomy can be considered
- Neck dissection following standard of care

Follow-up assessments (after treatment, through 2 years)
- Barium esophagram; dependence of a feeding tube, episodes of pneumonia and esophageal strictures should be checked and recorded; vocal-cord mobility; assessment of voice with a validated instrument; renal and hearing function at 6 months

End points
- Primary: laryngoesophageal dysfunction-free survival. Secondary: overall survival, progression-free survival, locoregional control, time to tracheotomy, time to laryngectomy, time to discontinuation of feeding tube and quality of life
- Translational research

Data taken from [52].

Toxicity & safety aspects

Treatment-related toxicity may compromise treatment delivery and may also be associated with life-threatening conditions in HNSCC patients. Consequently, supportive care is a core component of HNSCC treatment [61]. Dysphagia, mucositis, pain, dermatitis, myelossupression and renal and hearing damage are the most proeminent acute adverse events, typically appearing during (chemo-)radiation protocols [62].

Dysphagia with long-term dependence on feeding tubes and increased risk of aspirative episodes is probably the most relevant late toxicity and it is more frequent in patients with older age, advanced T-stage, and larynx/hypopharynx as primary sites [63].

Among the end points to be considered in designing HNSCC studies, those related to both acute and late treatment-related toxicities must be adequately recorded and reported. One good example is the definition of laryngoesophageal dysfunction-free survival in larynx-preservation studies [52].

Xerostomia is another cumbersome toxicity in those HSNCCs treated with RT. Amifostin is an approved agent for preventing xerostomia, but costs, toxicity (e.g., hypotension) and the need for intravenous administration prior to each RT fraction are difficult barriers to its current use in daily clinical practice [64]. Parotid-sparing intensity-modulated RT was shown to reduce the incidence of xerostomia and led to better saliva-secretion recovery and improvements in quality of life according to the Phase III PARSPORT study [65]. No differences were detected between groups in non-xerostomia late toxicities, locoregional control or overall survival, after 24 months.

Tools for quality of voice evaluation, as the recently described London Speech Evaluation Scale [66] must be incorporated in clinical studies, as well as more comprehensive swallowing evaluation methods [67]. Measuring quality of life is an important tool in the evaluation of the impact of the disease and its treatment in HNSCC studies. It may result in changes in treatment planning and rehabilitation. The questionnaires are multidimensional, evaluating the global and specific quality of life based on domains

that include many aspects (physical, functional and emotional, among others). The most commonly used questionnaires are well validated in many languages. These are the University of Washington – Quality of Life Questionnaire; the Functional Assessment of Cancer Therapy and the European Organization for Research and Treatment of Cancer questionnaires EORTC-QLQ C30 (core questionnaire) and HN35 (head and neck cancer module C30/H&N35) [68–70].

Prevention

It is also important to mention some aspects to be considered in preventive studies in HNSCC. Undoubtedly, quitting both tobacco and alcohol remains the most important primary-prevention strategy in HNSCC and recent reviews on this topic were recently published [71,72].

During the last 20 years, many agents have been or are currently being tested in chemopreventive studies, including retinoids, EGFR inhibitors, cyclooxygenase-2 inhibitors, green tea extract and PPAR-γ agonists. Their value either as primary prevention agents of HNSCC or even to decrease the incidence of second primary tumors – a significant source of morbidity and mortality in HNSCC patients – must continue to be explored in clinical trials. An excellent review has just been published on this topic [73]. The integration of well-validated biomarkers in these evaluations is also essential. Loss of heterozygosity at specific chromosomal sites stands out as the most consistent and extensively characterized molecular marker of HNSCC risk described to date [73]. Active surveillance using salivary biomarkers is an appealing strategy [74]. HPV vaccination as a primary preventive strategy in oropharyngeal SCC is also being investigated [75].

Conclusion

A recent metanalysis of individual patient data from 104 trials (22,744 patients), revealed that event-free survival is a better correlate with overall survival than locoregional control and could be used as a surrogate for overall survival to assess the treatment effect of radiotherapy and chemotherapy

Executive summary

Locally advanced head & neck squamous cell carcinoma
- Concurrent cisplatin-based chemoradiation remains as the standard treatment, but it is associated with considerable toxicity. The incorporation of biomarkers to improve patient selection and to predict treatment response and outcomes are unmet needs.

Oropharyngeal squamous cell carcinomas & human papillomavirus-related tumors
- Human papillomavirus-positive oropharyngeal quamous-cell carcinoma patients could be treated with less-toxic therapies, but this hypothesis must be tested in prospective studies.

EGFR-targeting agents
- Cetuximab has been incorporated in the treatment of head and neck squamous cell carcinoma (HNSCC). Stratergies to overcome treatment resistance, apparently related to signaling transduction pathways activated by IGF-IR, PI3K and c-Met, must be explored as core components of clinical studies.

Induction chemotherapy
- Head-to-head comparisons of upfront concurrent cisplatin-based chemoradiation and three-drug induction chemotherapy (docetaxel, cisplatin and 5-fluoruracil) are already in progress.

Larynx preservation
- Recommendations regarding the end points to be adopted in designing larynx-preservation trials, minimum needed assessments, the best candidates to this treatment, and the use of biomarkers, were recently published.

Adjuvant treatment
- Molecular markers to better patient selection must be developed, considering the high-toxicity rate of cisplatin-based chemoradiation in these patients.

Relapsed &/or metastatic HNSCC
- Despite some advances in platinum-sensitive tumors, as the combination of cetuximab, 5-fluoruracil and cisplatin, the incorporation of new agents for platinum-refractory disease is urgently needed.

Toxicity & safety aspects
- Treatment-related toxicity may compromise treatment delivery and may also be associated with life-threatening conditions in HNSCC patients. Consequently, supportive care is a core component of HNSCC treatment.

Prevention
- Quitting tobacco and alcohol remains as the most important primary prevention strategy in HNSCC. Chemopreventive agents are still considered in the context of clinical studies.

in randomized studies in locally advanced HNSCC [76]. Since locally advanced disease is the most common stage at diagnosis, event-free survival must be incorporated as a primary outcome. Treatment-related toxicities must also be incorporated among the main outcomes.

The incorporation of molecular targeted therapies (e.g., anti-EGFR) have been demonstrated as being clinically useful therapies in HNSCC. Well-designed studies with translational components will be helpful to test newer innovative agents in this disease.

Future perspective

The incorporation of molecular targeted therapies has been demonstrated as clinically useful in HNSCC, with overall survival gains and a favorable toxicity profile, as a consequence of well-designed studies with translational research end points exploring response predictors and prognostic factors.

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