End points for new agents in induction chemotherapy for locally advanced head and neck cancers

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More than 60% of patients diagnosed with squamous cell carcinoma of the head and neck present at a locally advanced stage. Although multimodality therapy has improved locoregional control, the 5-year survival rate of this population rarely exceeds 30%. In this review, we analyzed the impact of chemotherapy in the management of locally advanced head and neck cancer and we underline the potential benefit of induction chemotherapy. The Meta-Analysis of Chemotherapy in Head and Neck Cancer collaborative group has suggested a survival advantage of 5% at 5 years for platin–5-fluorouracil induction chemotherapy. We have analyzed cofactors that may affect the survival of head and neck patients and propose new end points for assessment of the efficacy of induction chemotherapy. The detrimental effect of second primary tumors on long-term results is stressed and we have suggested the use of overall 2-year survival as a surrogate end point for induction chemotherapy efficacy. Finally, we have examined the impact of new cytotoxic agents and present the promising results of new taxane-based combinations.

Key words: head and neck cancer, neoadjuvant chemotherapy, new drugs, new methodology, taxanes

Introduction

Head and neck cancer includes squamous cell carcinomas of the oral cavity, pharynx and larynx (SCCHN) and is the sixth most common form of cancer worldwide. Tobacco and alcohol consumption are etiological factors involved in the onset of SCCHN, which commonly affects middle-aged or older men. In 1990, the annual incidence was reported to be three per 100 000 men in the USA [1] and 16.7 per 100 000 in Europe, with six, 16, 20 and 35 per 100 000 patients in Finland, UK, Italy and France, respectively [2]. More than 60% of patients present with locally advanced stage III–IV SCCHN at diagnosis [3]. The 5-year survival rate ranges from 20% to 50% and 10% to 30% for stage III and IV SCCHN, respectively [4]. Curative treatment of locoregional advanced SCCHN, when possible, consists of surgery, often followed by radiation therapy and/or of exclusive radiotherapy. Operability is dependent on multiple parameters: the tumor–node–metastasis (TNM) stage, the anatomical disease extension, the expected post-operative morbidity (functional impairment), the patient’s general health status, the frequent concomitant tobacco-related illnesses, and the surgeon’s experience. In older trials, the median survival duration and overall 5-year survival rate attained in patients with unresectable disease treated with radiation therapy alone were 13.3 months and 18%, respectively. Only 30% of these patients were still alive at 3 years, and 60–70% of them had developed locoregional relapses and/or distant metastasis [5].

Historically, clinicians have had recourse to chemotherapy for palliative treatment of metastatic or recurrent disease. SCCHN proved to be a chemosensitive tumor. Combination cisplatin and continuous infusion 5-fluorouracil (5-FU) yielded higher response rates than single agents such as methotrexate, but failed to prolong survival in patients with metastatic disease [6, 7]. Chemotherapy was then added to surgery and/or radiotherapy for the management of localized SCCHN. The rationale was that treatment of a small tumor burden with chemotherapy would lead to better local control and its expected corollary, improved survival rates.

This review examines the role of chemotherapy in the management of locally advanced SCCHN, focusing on the following three topics: (i) benefits currently obtained with induction chemotherapy; (ii) relevant end points other than 5-year overall survival to demonstrate the efficacy of induction chemotherapy; and (iii) promising cytotoxic agents in the pipeline.

Current chemotherapy regimen for locally advanced SCCHN

During the last two decades, chemotherapy has been incorporated into the multimodality management of localized SCCHN,
as either induction or adjuvant treatment (before or after the definitive treatment of local disease by surgery and/or radiotherapy) or concomitantly with radiotherapy in various chemoradiotherapy strategies. Most of these studies were inconclusive or results were at variance. The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) collaborative group was founded to investigate the role of chemotherapy in the treatment of localized SCCHN [8]. This group performed a meta-analysis of both published and unpublished randomized trials, conducted between 1965 and 1993, comparing several local treatments (surgery alone, radiotherapy alone or surgery followed by radiotherapy) with or without chemotherapy. In these studies, chemotherapy was administered either as induction therapy, concomitantly with radiotherapy, or as adjuvant therapy. Updated individual data with a minimal follow-up of 5 years were collected and the overall 5-year survival was calculated in an intention-to-treat analysis. Other end points such as the response rate or disease-free survival (DFS) could not be analyzed. The main results are summarized in Table 1. Altogether, when the authors considered the 10850 patients from the 65 studies retained, they found a significant absolute survival advantage of 4% at 5 years. Adjuvant chemotherapy afforded no survival advantage. The results in the group who received concomitant chemoradiotherapy and induction chemotherapy are discussed below.

Benefits and limits of concomitant chemoradiotherapy

In the MACH-NC meta-analysis [8], a survival improvement of 8% at 5 years was observed when chemotherapy was administered concomitantly with radiotherapy. Most of these trials used a low-dose single agent as a radiosensitizer. However, it might have been more rational to use a truly cytotoxic combination regimen, because cytotoxic drugs may be capable of both radiosensitizing and directly affecting/eradicating tumor cells. Better local control might have been achieved and distant micrometastases might have been eradicated. In four recent trials in advanced SCCHN [9–12], the effects of radiotherapy alone were compared with radiotherapy delivered concomitantly with chemotherapy combining cisplatin and continuous infusion 5-FU. Better local control and survival were obtained in the chemoradiotherapy arm in all four trials, confirming the findings of the meta-analysis.

With more intensive chemoradiotherapy [13], a local control rate of over 90% was achieved at 3 years, but 17% of these patients presented distant metastases. The achievement of better locoregional control placed distant metastases at the forefront of clinical concerns. The fact that they need to be uppermost among clinical targets is corroborated by the high rate of micrometastasis in advanced SCCHN reported in autopsy series [14]. Despite optimal chemoradiotherapy there is still a 30% risk that patients presenting with N3 disease [15] or a high-grade histology [16] will develop distant metastases.

Better control of systemic disease is critical in a strategy aimed at improving the outcome of patients, and only drug dose escalation was likely to reduce the rate of distant metastases. Although the rate of acute toxicities such as grade 3–4 mucositis observed in 36–67% of the patients randomized in the chemoradiotherapy arm in the four trials mentioned above [9–12] was acceptable, it prohibited further dose escalation. The split-course design in a Head and Neck Intergroup trial lowered the intensity of radiotherapy and facilitated the administration of chemotherapy. However, a trend (P = 0.14) was observed towards a lower median survival duration (14 months) in the split-course radiotherapy arm compared with that in the single daily fraction radiotherapy arm (19 months). The loss in efficacy resulting from the split-course radiotherapy was not offset by using multi-agent chemotherapy [17].

With the concomitant approach, intensifying chemotherapy would have been far too toxic, while efficacy would be lost with less dose-intense radiotherapy. The only way to intensify systemic treatment appeared to be the administration of induction chemotherapy. The feasibility of this approach was tested in 58 patients with stage III and IV SCCHN. A brief 6-week course of induction chemotherapy with carboplatin/paclitaxel was well tolerated and active, and did not compromise subsequent concomitant chemoradiotherapy [18].

Results from the meta-analysis and from several additional randomized studies have demonstrated the superiority of concomitant chemoradiotherapy over radiotherapy alone for patients with advanced SCCHN. The efficacy of induction chemotherapy should now be tested in trials that would

<table>
<thead>
<tr>
<th>Trial category</th>
<th>No. of trials</th>
<th>No. of patients</th>
<th>Difference (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td>65</td>
<td>10850</td>
<td>+4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>8</td>
<td>1854</td>
<td>+1</td>
<td>0.74</td>
</tr>
<tr>
<td>Induction</td>
<td>31</td>
<td>5269</td>
<td>+2</td>
<td>0.10</td>
</tr>
<tr>
<td>Cisplatin + 5-fluorouracil</td>
<td>15</td>
<td>2487</td>
<td>+5</td>
<td>0.01</td>
</tr>
<tr>
<td>Other chemotherapy</td>
<td>16</td>
<td>2782</td>
<td>0</td>
<td>0.91</td>
</tr>
<tr>
<td>Concomitant</td>
<td>26</td>
<td>3727</td>
<td>+8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
compare concomitant chemoradiotherapy alone with induction chemotherapy followed by concomitant chemoradiotherapy.

Two decades of induction chemotherapy

Rationale and pilot phase II trials

The rationale underlying the use of induction chemotherapy is based on the postulate that drug delivery is expected to be better in untreated well-vascularized tumors, that micrometastatic disease would be nipped in the bud and that tumor shrinkage would occur before surgery and/or radiotherapy [19]. The response rate achieved in previously untreated patients [20, 21] was two-fold higher than in patients with metastatic or recurrent disease after surgery and/or radiotherapy [6, 7]. The regimen combining 100 mg/m² cisplatin at day 1 and 1000 mg/m²/day continuous infusion 5-FU over 5 days, developed at Wayne State University in Detroit, appeared to be the most effective regimen and became the gold standard in advanced SCCHN [22]. The conclusions [23] drawn from several phase II studies were that induction chemotherapy achieved objective tumor regression in 60–90% of the patients, with a clinical complete response (CR) in 20–50% of them [22, 24–27]. Adding high-dose leucovorin to the standard cisplatin–5-FU combination yielded promising results in two trials [28, 29], but the high rate of severe mucositis and some toxicity-related deaths mandated the use of a lower dose of leucovorin. No direct comparison with the Wayne State regimen has been performed to date.

Phase III trials and results of the MACH-NC meta-analysis

The encouraging tumor responses observed in phase II studies had to be confirmed in randomized trials. In the 1970s, agents such as methotrexate were administered alone, for a short duration, and sometimes the intra-arterial route was preferred [30, 31]. Since the 1980s, the Wayne State regimen has been tested in several large phase III trials. Despite higher response rates with standard cisplatin–5-FU than with the older combinations, evidence for improved survival in favor of induction chemotherapy was still lacking.

In the MACH-NC meta-analysis, data from 31 phase III trials comparing induction chemotherapy followed by loco-regional treatment with locoregional treatment alone, indicated no survival advantage at 5 years. The wide heterogeneity between these studies and the totally distinct chemotherapy regimens administered justified a split into two subgroups for further analysis.

In the 16 trials with cytotoxics other than cisplatin–5-FU, the agents used were bleomycin [30, 32], bleomycin with vincristine [31], various three- to five-drug regimens without platinum (e.g. bleomycin, doxorubicin, mitomycin, cyclophosphamide, methotrexate, 5-FU, hydroxyurea and various vinca alkaloids) [33–36], or various three- to five-drug regimens including cisplatin [37–45]. The number of cycles varied from one to four. Despite the analysis of 2782 patients, no survival advantage was detectable. This lack of efficacy was attributed to poorly efficient drugs often given at a low dose and for a short duration. Dose-intensity data were often unavailable. Response to chemotherapy was rarely reported and was not taken into account in the meta-analysis. Using chemotherapy offering low response rates delayed local treatment (surgery or radiotherapy), the deferral of which could have exerted detrimental effects on local control and survival.

In the subgroup of 15 trials in which the cisplatin–5-FU combination was used, the dose, schedule and duration of chemotherapy was sufficient to obtain an acceptable tumor response [46–56]. The individual results of the five largest studies [46–49, 55] with the standard cisplatin–5-FU combination are summarized in Tables 2 and 3. Most patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Chemotherapy</th>
<th>Locoregional treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewin et al. [46]</td>
<td>461</td>
<td>CDDP 100 mg/m² day 1</td>
<td>RT or S + RT</td>
<td>2-year OS 55 41 0.59</td>
</tr>
<tr>
<td>Depondt et al. [55]</td>
<td>324</td>
<td>CBDCA 400 mg/m² day 1</td>
<td>RT or S + RT</td>
<td>4-year OS 56 46 &gt;0.05</td>
</tr>
<tr>
<td>Dalley et al. [47]</td>
<td>280</td>
<td>CDDP 100 mg/m² day 1</td>
<td>RT, S or S + RT</td>
<td>2-year OS 60 53 0.54</td>
</tr>
<tr>
<td>Paccagnella et al. [48]</td>
<td>237</td>
<td>CDDP 100 mg/m² day 1</td>
<td>RT or S + RT</td>
<td>2-year OS 37 29 0.21</td>
</tr>
<tr>
<td>Domenge et al. [49]</td>
<td>174</td>
<td>CDDP 100 mg/m² day 1</td>
<td>RT</td>
<td>DFS n.a n.a &gt;0.05</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; CBDCA, carboplatin; CDDP, cisplatin; CT, chemotherapy; DFS, disease-free survival; n.a., not available; OS , overall survival; RT, radiotherapy; S, surgery.
received three cycles of induction chemotherapy. The overall response rate ranged from 57% to 80%, with a CR rate ranging from 19% to 48%. Whether response was evaluated clinically or by computed tomography scan is unknown. While no single study had a sufficiently strong statistical power to demonstrate a significant survival advantage, the meta-analysis unveiled a significant survival gain of 5% at 5 years in favor of the cisplatin–5-FU induction combination. However, as corroborative evidence was not obtained in a single large trial, the findings in favor of induction chemotherapy remained frail. The duration of chemotherapy was perhaps inadequate, since a proportional increase was observed in the CR rate with the number of cycles administered. In the study by Paccagnella et al. [48], 2, 7, 19 and 31% of patients randomized to received cisplatin–5-FU achieved a clinical CR rate after cycles 1, 2, 3 and 4, respectively. However, if 88% of the patients were able to receive three cycles of chemotherapy, only 73% did in fact receive four cycles. Despite a substantial amount of data, several questions remain open: the number of chemotherapy cycles and the degree of response to chemotherapy required for treatment success is still unknown.

**Efficacy of induction chemotherapy: the need for other end points**

Neoadjuvant chemotherapy is only part of a treatment strategy comprising chemotherapy, surgery and radiotherapy. So, the evaluation of efficacy and survival should include this entire strategy of cure. The survival of patients with locally advanced SCCHN is dependent on several parameters. The tumor characteristics, the patient’s general condition and the combined effect of each treatment modality (chemotherapy, surgery, radiotherapy) may all exert an impact on survival. Given the multiplicity of factors involved, the efficacy of induction chemotherapy cannot exclusively be reflected by overall survival even if its improvement remains the ultimate goal. This section is an in-depth analysis aimed at determining which, among the multiple parameters affecting overall survival of head and neck cancer patients, is capable of accurately assessing the efficacy of induction chemotherapy.

### Causes of death and 5-year overall survival

The consumption of alcohol and tobacco is responsible for severe co-morbidity such as ischemic heart disease and chronic obstructive pulmonary disease [57]. However, the occurrence of a second cancer is the factor that exerts the greatest influence on the poor long-term survival rates generally observed [57]. The annual incidence of a second primary cancer varies from 1.9% to 3.3% according to the figures reported in the following four studies:

1. The incidence of second primaries following laryngeal cancer was analyzed in the Surveillance, Epidemiology and End Results data base from 1973 to 1996 [58]. Of 20074 laryngeal cancer patients surviving at least 3 months, 3533 (17.6%) developed a second cancer. The actuarial risk of developing a second cancer was 26% at 10 years and 47% at 20 years and most of these second malignancies were head and neck, esophageal or lung cancer.

2. A total of 110 second primary cancers occurred in 928 patients in the Radiation Therapy Oncology Group (RTOG) studies [59]. The estimated risk of developing a second tumor was 10% within 3 years of radiotherapy, 15% within 5 years and 23% within 8 years.

3. In a recently closed randomized study of secondary chemoprevention [60], the yearly SCCHN recurrence rate was 2.9%. Among 1190 patients, 156 second primary tumors had developed. The rates of a second primary among current, former and never smokers were 4.2, 3.1 and 1.6%, respectively. This rate was significantly higher among smokers versus non-smokers (P = 0.008).

4. The Euroscan secondary prevention trial [57] randomized 2592 patients with head and neck cancer (60%) or with lung cancer (40%), most of whom were former or current smokers. Two years of retinyl palmitate and/or N-acetylcysteine supplementation afforded no benefit in terms of survival, event-free survival, or the incidence of second primary tumors. The annual incidence of second primary tumors was 1.9%.

Carcinogenesis is a multistep process occurring over many years and until now only smoking cessation has proven an effective counter measure. As there are no effective drugs

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**Table 3. Objective response rate to induction cisplatin–5-FU chemotherapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Evaluable patients (n)</th>
<th>Response rate to CT alone or CT + RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>CR rate (%)</td>
</tr>
<tr>
<td>Lewin et al. [46]*</td>
<td>CT + RT</td>
<td>215</td>
<td>48</td>
</tr>
<tr>
<td>Depondt et al. [55]</td>
<td>CT + RT ± S</td>
<td>143</td>
<td>31</td>
</tr>
<tr>
<td>Dalley et al. [47]</td>
<td>CT + RT ± S</td>
<td>140</td>
<td>32</td>
</tr>
<tr>
<td>Paccagnella et al. [48]</td>
<td>CT + RT ± S</td>
<td>112</td>
<td>31</td>
</tr>
<tr>
<td>Domenge et al. [49]</td>
<td>CT + RT</td>
<td>79</td>
<td>19</td>
</tr>
</tbody>
</table>

*Only the response rate after radiotherapy is available.

CR, complete response; CT, chemotherapy; PR, partial response; RT, radiotherapy; S, surgery.
designed to prevent carcinogenesis of the aerodigestive tract, chemotherapy is unlikely to have an influence on the long-term rate of second primary tumors in patients with head and neck cancer. This excess mortality unrelated to the first SCCHN strongly diminished the anticipated long-term survival advantage due to treatment of the primary tumor. The 5-year overall survival rate can thus only be a blended yardstick of the efficacy of induction chemotherapy.

**DFS and 2-year overall survival**

We have discussed that overall survival at 5 years may not distinguish the causes of mortality due to second cancers and tobacco-related diseases. The 5-year specific DFS could be a good parameter, but it is sometimes uncertain whether a new cancer of the head and neck is a second primary or a recurrence. Time to treatment failure may be useful in differentiating these lesions. In an RTOG study [61] of patients treated by surgery and radiotherapy for a supraglottic larynx or hypopharynx cancer, up to 80% of the local recurrences occurred within the first 2 years. After 2 years, distant metastases and second primaries became the predominant cause of failure.

DFS at 2 years may thus be a good yardstick of treatment-induced disease control. However, in the case of locally advanced SCCHN, disease is frequently persistent and patients with such disease are not taken into account in the calculation of DFS. Patients with refractory SCCHN die soon after the beginning of treatment. During the first 2 years, death can be caused by treatment-related toxicity, persistent disease or an early relapse. The cause of death in the induction chemotherapy arm in the trial reported by Paccagnella et al. [48] is, however, manifest. Less than 60% of patients achieved a CR at the end of the treatment and of them, 70% presented a local relapse at 2 years. The 2-year overall survival rates, which were 56% and 30% for operable and inoperable patients, respectively, very accurately reflect this dismal outcome. Two-year overall survival therefore appears to be correlated with the overall efficacy of chemotherapy and could be used as a surrogate end point of the activity of induction chemotherapy.

**Response rate and its evaluation**

The assessment of response has evolved over the years and comparison of response rates in recent phase II trials with large historical series remains a hazardous endeavor. The response rates reported probably overestimated the tumor response, which is currently evaluated by computed tomography scan or magnetic resonance imaging. Modern imaging techniques demonstrate residual disease in patients supposedly in complete remission according to clinical examination. The MACH-NC meta-analysis was not able to provide information on the techniques used for tumor evaluation. In Table 3, we have summarized rates of response to induction chemotherapy and the method of evaluation of the five largest studies using cisplatin–5-FU. Overall response rates ranged from 57% to 80% (CR 19–48%). Antitumor activity was evaluated mostly by clinical examination. In these studies, there was no comparison of outcome between patients achieving a CR and patients in whom this was not achieved following induction chemotherapy.

Pathological examination of operative or biopsy specimens after chemotherapy seems to be more accurate than clinical evaluation alone. If a CR is reflective of chemosensitivity, patients who achieve a complete pathological response (pCR) in the primary tumor after induction chemotherapy should have a better prognosis than patients with suboptimal responses. This hypothesis has been demonstrated in patients with locally advanced breast cancer: achieving a pCR following induction chemotherapy had a favorable impact on DFS [62]. The team at Wayne State University conducted three consecutive pilot studies between 1977 and 1982 of patients with locally advanced SCCHN, and reported on the outcome of 191 patients who were treated with cisplatin, vincristine and bleomycin or cisplatin–5-FU before definitive surgery or radiation [22]. A 39% clinical CR rate (74 patients) was achieved. Thirty-two of the complete responders to chemotherapy underwent radical surgery. No histological evidence of residual disease was found in the operative specimens in 13 of them. All patients with a histologically confirmed CR were clinically free of disease at a median follow-up of 36 months. The survival of patients who achieved both a clinically and histologically proven CR was superior to that of patients whose CR was confirmed clinically alone and in whom residual tumor was found in the operative specimen (P = 0.01). In another series [63] of 152 patients who received two or three courses of induction chemotherapy, CR was the most significant prognostic factor, more so than age, performance status (PS), tumor size and nodal status in a multivariate analysis. The long-term follow-up of the organ-preservation trial conducted by the Veterans’ Affairs Cooperative Laryngeal Cancer Study Group [64] has also demonstrated better survival for patients who had achieved a pCR.

Evaluation of the response to a single cycle of induction chemotherapy can also be used as a selector of patients who will respond to subsequent chemoradiotherapy. In a recent study by Urba et al. [65], 52 patients with stage III or IV laryngeal cancer received one cycle of cisplatin–5-FU. Thirty-six patients who achieved a >50% reduction of tumor were assigned concurrent chemoradiation; those with a <50% response underwent salvage surgery. Of the 36 patients who underwent chemoradiation, 32 were complete histological responders. One cycle of induction chemotherapy can predict a group of patients who are very sensitive to chemoradiation for larynx preservation.

As not all head and neck patients undergo surgery, particularly if response to chemotherapy is complete, pathological evaluation of response will not necessarily be available in future trials. Confidence must therefore be preserved in the clinical and radiological evaluation of response.
Other unproven surrogate end points

Of interest are new radiological tools that can be used to identify and evaluate response to induction chemotherapy earlier. This early radiological evaluation of response would avoid prolonging chemotherapy unnecessarily in patients with refractory disease or poor responders, and salvage surgery could be offered as an alternative to radiotherapy because it has been demonstrated that patients with chemoresistant disease respond poorly to radiotherapy [66]. Among the new radiological methods are the measurement of computed tomography density of nodal disease in patients treated by radiochemotherapy [67], sestamibi Tc 99m single-photon emission tomography in patients with nasopharyngeal carcinoma treated by radiotherapy [68] and a positron emission tomography scan in patients with larynx carcinoma treated by radiochemotherapy [69]. However, the predictive value of these techniques has yet to be validated in patients receiving induction chemotherapy.

Targeting treatment to tumor characteristics is a long-standing hope in medical oncology that has not been accomplished. Some recent retrospective studies in head and neck cancer patients have shown a negative correlation between the presence of p53 mutations in tumor tissue and response to cisplatin [70, 71]. Future trials should not only assess the activity of new chemotherapeutic agents, but should also include a prospective evaluation of new biological predictive factors.

The challenge for the improvement of induction chemotherapy will be to establish selection criteria of the patients based on their tumor characteristics and to develop new drug combinations to increase the complete tumor response rate.

New agents in the pipeline

We have noted that despite high local control rates achieved with intensive chemoradiotherapy, distant failure has become a major cause of death, for which more effective chemotherapy is advocated. The induction setting appears to be more conducive to better drug delivery to the tumor as blood vessels are still intact and have not been exposed to radiation-induced damage. The new drug combinations should ideally obtain high response rates in the shortest possible time, without compromising subsequent treatment due to prolonged or delayed toxicities.

Several phase II trials have evaluated the efficacy of novel cytotoxic agents in patients with recurrent or metastatic SCCCHN [72]. The single agent activity of gemcitabine [72], vinorelbine [73, 74] and topotecan [75] continued to be disappointingly limited to an overall response rate short of 20%. Only Caelyx (pegylated liposomal doxorubicin) yielded a response rate of 33% in 24 patients [76]. The taxanes appeared to be the most promising drugs and the preliminary results of induction chemotherapy with paclitaxel and docetaxel are discussed below.

Paclitaxel

Single agent paclitaxel [77, 78] at a dose of 250 mg/m²/24 h with granulocyte colony-stimulating factor (G-CSF) supports attained response rates ranging from 36% to 40% in patients with recurrent or metastatic disease. A combination of paclitaxel with carboplatin [79] or cisplatin [80] achieved higher response rates of 32% and 78%, respectively. Neutropenia was the main toxicity documented in ∼90% of the patients.

Paclitaxel is a known radiosensitizer and several chemoradiotherapy phase II studies have included paclitaxel, either alone or in combination with carboplatin [81, 82]. A promising clinical CR rate at the primary site attaining 82% was reported for 62 patients with an unresectable disease treated by concomitant paclitaxel–carboplatin and radiotherapy [82].

Paclitaxel-containing induction chemotherapy has been evaluated in two-drug combinations reported by Vokes et al. [18] (Table 4) and three-drug combinations reported by Papadimitrakopoulou et al. [83] (Table 5). Both trials obtained impressive objective response rates exceeding 80% in patients with advanced disease (>80% stage IV). The weekly carboplatin–paclitaxel schedule in Vokes’ trial was well tolerated, with toxicities limited to grade 3 neutropenia and grade 1–2 neuropathy in 20% and 38% of the patients, respectively. No complications deferred the delivery of subsequent chemotherapy.

### Table 4. Objective response rate to induction chemotherapy with two-drug combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy dosage and schedule</th>
<th>Activity</th>
<th>No. of patients</th>
<th>CR (n)</th>
<th>PR (n)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vokes et al. [18]</td>
<td>P 135 mg/m² day 1, Ca AUC 2 day 1 q 1 week for 6 cycles</td>
<td>46</td>
<td>13</td>
<td>24</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Manzione et al. [89]</td>
<td>D 75 mg/m² day 1, C 100 mg/m² day 1 q 3 weeks for 3 cycles</td>
<td>26</td>
<td>4</td>
<td>8</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Mel et al. [88]</td>
<td>D 75 mg/m² day 1, C 75 mg/m² day 1 q 3 weeks for 3 cycles</td>
<td>37</td>
<td>11</td>
<td>9</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Biakho et al. [90]</td>
<td>D 75 mg/m² day 1, C 75 mg/m² day 1 q 3 weeks for 3 cycles</td>
<td>37</td>
<td>6</td>
<td>14</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D 85 mg/m² day 1, F 750 mg/m² c.i.v. day 1–5 q 3 weeks for 3 cycles</td>
<td>35</td>
<td>7</td>
<td>12</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

Tumor evaluation was done after induction chemotherapy and before local treatment.

AUC, area under the curve; C, cisplatin; c.i.v., continuous intravenous infusion; Ca, carboplatin; CR, complete response; D, docetaxel; F, 5-fluorouracil; L, leucovorin; n.a., not available; ORR, overall response rate; P, paclitaxel; p.o., per os; PR, partial response.
chemoradiotherapy. Data on the pathological response rate and on survival are not available.

**Docetaxel**

Single-agent docetaxel at a dose of 100 mg/m² demonstrated overall response rates of 21–42% in patients with recurrent or metastatic disease [84–86]. Therefore, docetaxel and cisplatin were placed among the most active antitumor agents in head and neck cancer. This two-drug combination was demonstrated to be feasible in phase I studies. The combination of docetaxel 100 mg/m² and cisplatin 75 mg/m² produced an overall response rate of 54% among 41 evaluable patients with locally advanced, recurrent or metastatic SCCHN [87]. Hematological and non-hematological toxicities were common.

Induction chemotherapy with docetaxel-containing regimens has only been evaluated in phase II trials, reported mostly in abstract form (see Tables 4 and 5).

**The two-drug combination**

Combination of docetaxel 75 mg/m² and cisplatin 75 mg/m² [88] or 100 mg/m² [89] has achieved a response rate of 54% and 46%, respectively, in patients with inoperable advanced SCCHN. The higher dose of cisplatin caused more febrile neutropenia (15% versus 7%), and four deaths occurred during the induction phase in the trial conducted by Manzione et al. [89].

In a Russian randomized phase II study [90] comparing an induction docetaxel–cisplatin regimen with docetaxel–5-FU in patients with locally advanced SCCHN, no statistically significant differences were observed for activity and toxicity. The two-drug combination has not produced higher response rates than the standard cisplatin–5-FU combination.

**The three-drug combination**

Three trials have investigated the addition of docetaxel to standard cisplatin–5-FU. After inclusion of 13 patients treated with cisplatin 75 mg/m² (level I) in a multicenter North-American phase II study in patients with locally advanced SCCHN [91], an escalated dose of cisplatin 100 mg/m² was administered to the 17 subsequent patients (level II). Impressive overall response rates of 84% and 100% were reported for level I and II, respectively. Severe mucositis was reported in 14% of the cycles. All patients received oral prophylactic antibiotherapy.

A European phase I/II trial in patients with locally advanced inoperable SCCHN [92] also escalated the cisplatin dose from 75 mg/m² (level I, at which 17 patients were included) to 100 mg/m² (level II, at which 11 patients were included). Tumor evaluation was performed only after local treatment with radiotherapy and demonstrated an overall local control of 80%. Mucositis and diarrhea were the most frequent toxicities. Prophylactic antibiotherapy with ciprofloxacin was administered to reduce the rate of infectious complications.
Finally, a Greek trial with a more limited number of patients [93] reported an overall response rate of 90% after a median of three cycles of docetaxel, cisplatin and 5-FU in 20 patients with locally advanced SCCHN.

The head and neck team at the Dana Farber Cancer Institute published reports on three trials testing the adjunction of docetaxel to a continuous infusion of combination cisplatin, 5-FU and high-dose leucovorin in patients with locally advanced SCCHN.

The first phase I/II trial [94] established the maximum tolerated dose (MTD) of docetaxel at 60 mg/m² in combination with a 5-day infusion of cisplatin, 5-FU and high-dose leucovorin (TPFL5) that was followed by radiotherapy delivered twice daily. The rate of overall response to TPFL5 was 100%. However, despite prophylactic administration of intravenous fluids, antibiotics and G-CSF, a high rate of severe neutropenia, mucositis, diarrhea, peripheral neuropathy and sodium-wasting nephropathy led to the hospitalization of patients in 35% of treatment cycles.

A shorter induction chemotherapy regimen (TPLF4, described in Table 5) [95], was designed to introduce supportive measures such as antibiotics and G-CSF earlier. The need for hospitalization for toxicity was reduced by half. The overall response rate remained close to 100%. A remarkable pCR rate was achieved in 15 of 22 postchemotherapy biopsies. No data are available on survival.

The same group [96] modified the cisplatin administration schedule, replacing the 4-day infusion by a 1-h infusion at day 1. This new phase I trial (OP-TPFL) was able to escalate the dose of docetaxel up to 90 mg/m². The main grade 3–4 toxicities observed at the MTD in 15 patients were neutropenia and mucositis in 17 of 42 and 11 of 42 cycles, respectively. The overall response rate remained at 94%.

Future directions with docetaxel-containing induction chemotherapy

Adding docetaxel to cisplatin–5-FU or cisplatin–5-FU–leucovorin regimens produced response rates exceeding 80% in all these phase I/II trials. However, the toxicities observed render intensive supportive care (prophylactic antibiotics, G-CSF and feeding tubes) necessary. Such intensive regimens should probably be restricted to patients with a good PS. Good tolerance was observed with weekly docetaxel and its activity was maintained in patients with metastatic breast cancer [97] and non-small-cell lung cancer [98]. Weekly docetaxel can also be combined with carboplatin [99] and should also be tested as induction chemotherapy in advanced SCCHN, as is already the case with the weekly paclitaxel–carboplatin combination [100].

Although the reported activity of all these phase II trials is remarkably high, these results should be considered only as preliminary. Patients with a locally advanced SCCHN form an extreme heterogeneous population and large variations in the response rate at the primary site can be observed between T3 or T4 stages. This well-known effect of patient selection can only be alleviated by the realization of randomized trials. Definitive data concerning the activity and the toxicity of the taxanes included in induction chemotherapy can only be derived from the results of phase III trials.

Two ongoing phase III studies are testing the value of docetaxel in induction chemotherapy. The European Organization for Research and Treatment of Cancer (EORTC) 24971 is a phase III multicenter trial of induction docetaxel plus cisplatin–5-FU versus induction cisplatin–5-FU in patients with locally advanced inoperable SCCHN. The sample size is 348 patients. The US National Cancer Institute is running a phase III trial with similar design. The results of these studies are eagerly awaited to confirm the hope that the taxanes have rekindled in induction chemotherapy for the management of advanced SCCHN. However, the design of these two studies will not help to establish the effect on survival of the addition of induction chemotherapy to conventional chemoradiotherapy, because induction chemotherapy is a part of the treatment strategy in both arms of these trials.

Conclusions

Despite more than 20 years of clinical research, induction chemotherapy for locally advanced SCCHN remains a controversial issue. However, the following points can be retained as practical guidelines for the management of patients with advanced head and neck cancer and to help clinicians design new trials:

- Good local control is achieved with concomitant chemoradiotherapy but it does not prevent the occurrence of distant metastasis, which has become the main clinical challenge.
- Induction chemotherapy with the cisplatin and continuous infusion 5-FU combination is associated with a survival advantage of 5% at 5 years.
- In evaluating new induction chemotherapy, end points such as the CR rate and the early 2-year overall survival rate could be used as the main surrogate markers of activity.
- Taxane-based combinations are the most promising induction chemotherapy regimens and are now being tested in randomized trials.
- The delivery of induction chemotherapy generally does not hamper further local treatment such as chemoradiotherapy and surgery.
- Biological studies of predictive factors and early radiological assessment of tumors warrant further investigation in a prospective fashion.
- Research should be pursued to decrease the excess mortality due to a second primary cancer and co-morbidity.

Advanced head and neck cancer remains a therapeutic challenge and the collaboration of multidisciplinary teams is, more than ever, essential. The technological development of new radiological and biological tools, coupled with the intro-
duction of new cytotoxic compounds and biological agents may offer encouraging possibilities to clinical investigators.

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References


