Symposium article

New approaches to enhance chemotherapy in SCCHN

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Chemotherapy is the standard approach to the treatment of patients with recurrent and metastatic squamous cell carcinoma of the head and neck (SCCHN) and is also now a common component of treatment for patients with locoregionally advanced, non-metastatic disease. Cisplatin has for many years been the agent of choice, alone or in combination with other agents, particularly 5-FU. The advent of the taxanes, which demonstrate good non-clinical activity against SCCHN, spawned a series of investigations aimed at integrating these agents into treatment regimens. Molecular targeted agents, which do not demonstrate overlapping toxicities with commonly used chemotherapy agents for SCCHN, represent a promising avenue of investigation. The epidermal growth factor receptor (EGFR) is expressed both widely and at high levels in SCCHN and is associated with poor prognosis. The EGFR-directed monoclonal antibody (MAb) cetuximab (Erbitux®) in combination with chemotherapy has shown some activity in the treatment of recurrent/metastatic disease both as first-line therapy and following cisplatin failure, and preliminary results suggest single-agent activity in platinum-resistant disease. Promising activity has also been observed with a number of other EGFR inhibitors, both MAbs and tyrosine kinase inhibitors.

Key words: cetuximab, chemotherapy, EGFR, SCCHN

Introduction

Cisplatin-based regimens are the standard approach to chemotherapy used in the post-operative setting for resectable disease, for locally advanced unresectable disease and by many also considered standard for the first-line treatment of recurrent/metastatic disease. In general, two-agent regimens are preferred, at least for unresectable and recurrent/metastatic disease, and 5-fluorouracil (5-FU) is often the combination agent of choice. This paper focuses on current and potential chemotherapy options for use in the management of locally advanced unresectable disease and recurrent/metastatic disease.

Chemotherapy for recurrent/metastatic disease

Chemotherapy is the mainstay of treatment for patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN). The benefits of cisplatin were shown nearly 20 years ago [1] and it is probably the most important agent. Survival benefits of 10 weeks may be expected [1]. The dose-limiting toxicities associated with cisplatin are well documented and include haematological toxicity, neurotoxicity, nephrotoxicity and ototoxicity. Attempts to deliver higher-dose or dose-intensified cisplatin have largely been unsuccessful due to these toxicities. A randomized study by the European Organization for Research and Treatment of Cancer demonstrated that concurrent administration of amifostine reduced the risk of toxicity but did not enable cisplatin dose intensification [2]. Randomized trials have shown increased response rates but failed to show a survival benefit for cisplatin in combination with 5-FU or methotrexate over single-agent therapy [3–6]. Despite this, for patients who are able to tolerate more aggressive chemotherapy than standard methotrexate, combination chemotherapy with a cisplatin-based regimen is used by many as a standard approach for patients with recurrent/metastatic disease. With the advent of newer therapies over the last ten years, attempts to improve outcome to chemotherapy have continued. The taxanes are now an integral part of therapy for a number of different tumour types and are active in SCCHN. However, the results in the first-line setting are conflicting and on the whole disappointing. The Eastern Co-operative Oncology Group study conducted two randomized phase III studies with paclitaxel in combination with cisplatin. The first study involved the addition of high- or low-dose paclitaxel to cisplatin [7]. This study showed no survival advantage of high-dose paclitaxel, but an excess of haematological toxicity: 70% of those receiving high-dose paclitaxel and 78% receiving low-dose paclitaxel developed grade 3/4 neutropenia, despite the use of granulocyte-colony stimulating factor in those receiving high-dose paclitaxel. In the second study, the combination of cisplatin and paclitaxel was no more effective, in terms of response and survival, than cisplatin and 5-FU, but was less toxic in terms of both haematological and non-haematological toxicity [8]. A number of phase II trials have shown that...
combinations of docetaxel and cisplatin or paclitaxel and carboplatin show activity in metastatic disease, although prophylaxis to reduce haematological toxicity may be required [9, 10]. More recently, a phase II study suggested that a schedule of dose-dense weekly administration of reduced individual doses of paclitaxel in combination with carboplatin may be better tolerated [11]. The response rate of 60% achieved with this regimen suggests that it may be worth pursuing. Vinorelbine has also shown moderate activity as a single agent in the first-line treatment of recurrent/metastatic SCCHN [12]. An attempt to modulate the combination of cisplatin/5-FU with the biological response modifier interferon-α-2b failed to show any clinical benefits in a phase III trial [13].

The prognosis of patients with recurrent/metastatic SCCHN who progress on platinum-based chemotherapy is poor and these patients have only limited alternative therapeutic options. A retrospective analysis of 151 patients relapsing on platinum-based therapy who then received second-line chemotherapy, radiotherapy or best supportive care showed the median survival of this group to be only 3.5 months [14]. Of the 57 patients receiving second-line chemotherapy (including platinum, methotrexate, bleomycin or docetaxel, either alone or as part of a combination regimen) only 3% achieved a response [14]. The use of novel combinations of chemotherapy have been investigated in a number of small phase I/II studies (Table 1) [15–19]. The combination of vinorelbine with cisplatin, docetaxel or gemcitabine has shown some activity in patients with SCCHN, a proportion of whom had received previous chemotherapy [15–17]. A combination of capecitabine and cisplatin has also been shown to be feasible in a similar patient population [19]. However, improvements in survival appear limited and generally the outlook for patients failing on platinum therapy remains dismal.

**The benefits of chemotherapy in loco-regional disease**

The benefit of adding chemotherapy to locoregional therapy for non-metastatic disease was confirmed by the results of a meta-analysis of 87 trials conducted by our group (meta-analysis of chemotherapy in head and neck cancer, MACH-NC collaborative group) [20]. This analysis included more than 16,000 patients. Overall, there was a statistically significant survival benefit of 5% at 5 years for the use of chemotherapy ($P < 0.0001$).

There was also a significant interaction between the timing of chemotherapy and survival ($P < 0.0001$). In 50 of the trials, chemotherapy was given concomitantly with radiotherapy and in these trials, the absolute benefit was 8% at 5 years ($P < 0.0001$). The type and timing of radiotherapy (conventional and altered fractionated radiotherapy, whether definitive or post-operative) used with chemotherapy did not influence the outcome. Also, there was no significant difference in survival between the use of monotherapy or combined chemotherapy. However, the greatest benefit was seen with platinum-based chemotherapy compared with other chemotherapy ($P < 0.01$). These results confirmed those of our previous, smaller analysis [21] and those of a review by Browman et al. [22]. In a pooled analysis of 18 randomized trials, involving 3,192 patients with locally advanced disease, Browman and colleagues reported an 11% reduction in the risk of death with the use of concomitant chemotherapy compared with radiotherapy alone ($P < 0.00001$). Platinum-based regimens were the most effective of the chemotherapy regimens used ($P < 0.00001$). The addition of chemotherapy concomitant with radiotherapy generally results in significant acute and late toxic effects [23]. Given the improved anti-tumour efficacy associated with the addition of chemotherapy, optimisation is needed to improve the tolerability of the combined treatment. With that in mind, intensity modulated radiotherapy could be a useful tool, decreasing the dose of radiotherapy delivered to normal tissues, while increasing the dose in the gross tumour volume. The use of new drugs, especially of targeted therapies that are associated with a relatively good tolerability profile, might also be of interest in terms of minimising side effects in combination with radiotherapy while maintaining antitumour efficacy [24].

The value of neoadjuvant therapy in SCCHN remains to be confirmed [25]. However, recent data with the taxanes is encouraging, and the addition of docetaxel or paclitaxel to cisplatin/5-FU appears to be a particularly promising approach [26, 27]. We recently reported an analysis comparing data from six phase II trials using the combination of docetaxel/cisplatin/5-FU ($n = 195$) as neoadjuvant therapy with data from five large randomized trials using platinum/5-FU ($n = 585$) (derived from the MACH-NC database) [28]. Patients received radiotherapy and/or surgery following chemotherapy. A patient selection standardisation method and Cox model were used to adjust for potential selection bias. The addition of docetaxel to treatment was associated with a significantly reduced risk of death: the relative

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. patients</th>
<th>Previous chemotherapy</th>
<th>Response rate</th>
<th>Median overall survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine + cisplatin</td>
<td>42</td>
<td>$n = 2$</td>
<td>33%</td>
<td>6 months</td>
<td>Espinosa et al. 2002 [15]</td>
</tr>
<tr>
<td>Vinorelbine + gemcitabine</td>
<td>24</td>
<td>$n = 14$</td>
<td>25%</td>
<td>9 months</td>
<td>Airoldi et al. 2003 [16]</td>
</tr>
<tr>
<td>Vinorelbine + docetaxel</td>
<td>29</td>
<td>$n = 15$</td>
<td>49%</td>
<td>10 months</td>
<td>Airoldi et al. 2003 [17]</td>
</tr>
<tr>
<td>Capecitabine + cisplatin</td>
<td>21 (17*)</td>
<td>All</td>
<td>41%</td>
<td>7.3 months</td>
<td>Pivot et al. 2003 [19]</td>
</tr>
<tr>
<td>Permetrexed</td>
<td>35</td>
<td>$n = 14$</td>
<td>27%</td>
<td>7.3 months</td>
<td>Pivot et al. 2001 [18]</td>
</tr>
</tbody>
</table>

*Evaluable for response.*

Table 1. Novel chemotherapy combinations for the treatment of metastatic/recurrent SCCHN
risk of death was 1.85 in the platinum/5-FU arm in relation to the docetaxel/platinum/5-FU arm. This corresponded to a significant 2-year survival benefit of 20% ($P < 0.0001$). These results were confirmed by a randomized trial from the EORTC involving 358 patients with unresectable locally advanced SCCHN demonstrating a significant improvement in outcome with the addition of docetaxel to platinum/5-FU prior to radiotherapy. At a median follow-up of 32 months, the docetaxel group demonstrated significantly prolonged progression-free survival ($P = 0.006$) and overall survival ($P = 0.016$) and a higher response rate (68% vs. 54%, $P = 0.007$). The docetaxel regimen also appeared to be better tolerated and was associated with fewer toxic deaths (5% vs. 2%) [29].

**Targeted therapies in combination with chemotherapy**

The combination of standard chemotherapy with molecular targeted therapy is an attractive proposition for improving response to treatment. Such agents offer a way of directly targeting the tumour without exacerbating the side effects associated with standard chemotherapy.

The epidermal growth factor receptor (EGFR) has been identified as an important target for cancer therapy. It is expressed at high levels in a number of tumour types and in most SCCHN [30], and is associated with an adverse impact on survival [31]. Inhibition of the EGFR, most commonly using monoclonal antibodies (MAbs) directed against the external ligand binding domain or small molecule tyrosine kinase inhibitors, has been the focus of much attention in recent years. Cetuximab is an IgG1 MAb that specifically targets the EGFR and inhibits signal transduction [32, 33]. Cetuximab is approved in Europe and the US for use in patients with EGFR-expressing metastatic colorectal cancer. Its use in head and neck cancers was a logical step in view of the expression of EGFR in a high proportion of SCCHN.

A series of studies have shown the activity of cetuximab in the treatment of recurrent/metastatic disease both as first-line therapy and following platinum failure.

In a randomized phase III trial in the first-line setting, 118 patients were randomized to receive cisplatin 100 mg/m$^2$ q28 days plus either cetuximab (400 mg/m$^2$ on day 1 followed by subsequent weekly doses of 250 mg/m$^2$) or placebo [34]. There was a significantly higher response rate among those patients receiving cetuximab (26% vs 10%, $P = 0.048$). Although there was no significant difference between the medians of progression-free survival (4.2 vs 3.4 months) and overall survival (9.3 vs 8.0 months) between the arms, there did appear to be a survival advantage for patients developing skin toxicity ($P = 0.011$).

The most common grade 3/4 abnormalities were those expected with cisplatin chemotherapy. However, grade 3 rash, a characteristic side effect of EGFR inhibitors, was seen in 17% of patients receiving cetuximab but in none receiving placebo. Preliminary data from a phase I study in the first-line setting showed that the addition of cetuximab to a combination of cisplatin/carboplatin and 5-FU was well tolerated in the first-line setting and demonstrated encouraging activity [35].

The dismal prognosis of patients failing on first-line platinum-based therapy is well known. The combination of cetuximab and cisplatin or carboplatin in patients with SCCHN that had progressed on cisplatin-containing therapy was investigated in two phase II studies (Table 2) [36]. In a US study, a partial response rate of 12% was observed. A similar European study in 96 patients reported an overall response rate of 15%, with two complete and 12 partial responses [37]. A further 38 patients (40%) had stable disease or minor responses lasting for at least 6 weeks. The median survival was 5.9 months overall and 8.5 months in responding patients. The response rates (12% and 15%) observed in these two studies are encouraging in view of the 3% that has previously been reported for such patients.

Single-agent cetuximab has also shown significant activity in disease failing on platinum-based therapy. Preliminary findings with cetuximab monotherapy in 103 patients with documented progression of metastatic disease showed a response rate of 17% and clinical benefit (partial response + stable disease) in 53% of cases (Table 2) [38]. The median time to progression was 85 days and the median survival 175 days. These findings are encouraging and in line with those reported for cetuximab in combination with cisplatin.

Anti-tumour activity has also been seen with a number of other EGFR inhibitors. The humanized MAb h-R3 [39, 40] and the rat MAb ICR-62 [41], which are both at an earlier stage of development than cetuximab, have shown activity against SCCHN cells and are currently being investigated in early clinical trials.

**Table 2. Cetuximab alone or in combination with platinum-based therapy in recurrent/metastatic SCCHN progressing on platinum-containing therapy**

<table>
<thead>
<tr>
<th>Treatment regimen cetuximab</th>
<th>Response rate</th>
<th>Disease control rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%a</td>
<td>n</td>
</tr>
<tr>
<td>+ cisplatin</td>
<td>9/78</td>
<td>12% [5.9–20.4]</td>
<td>22/78</td>
</tr>
<tr>
<td>+ cisplatin/carboplatin</td>
<td>14/96</td>
<td>15% [8.3–23.1]</td>
<td>52/96</td>
</tr>
<tr>
<td>Monotherapy$^b$</td>
<td>17/103</td>
<td>17% [9.9–25.1]</td>
<td>55/103</td>
</tr>
</tbody>
</table>

$^a$Data are presented as % and [95% confidence intervals] where available from reference.

$^b$Preliminary efficacy data based on investigator assessment. See text for details of doses.
The tyrosine kinase inhibitors erlotinib [42, 43] and gefitinib [44, 45] have also shown activity in phase II trials in SCCHN. Finally, given the complex nature of cellular signaling and the array of pathways involved, possible additional targets for novel SCCHN therapies include; DNA repair proteins, signal transduction pathways (farnesyl transferase inhibitors, PKC inhibitors), proteins involved in cell cycle regulation (cyclin-dependent kinases), proteosomes and angiogenesis.

Conclusions
Chemotherapy remains an integral part of treatment for recurrent and metastatic SCCHN and has also been confirmed as a major component of therapy for many patients with locoregionally advanced disease. However, while chemotherapy is clearly a valuable tool, it is nearly 20 years since cisplatin was identified as the gold standard of treatment and optimum treatment regimens should be defined in the light of new agents and those with novel modes of action. The taxanes have emerged as some of the most active agents for SCCHN, that need further investigation. An additional promising approach is the use of molecular targeted agents, such as the EGFR inhibitor cetuximab, which generally do not have the dose-limiting side effects associated with standard chemotherapeutic agents. To date, clinical trials have shown the activity of cetuximab in combination with chemotherapy in the first-line treatment of recurrent/metastatic disease and in patients with platinum-resistant disease. Of particular interest are the preliminary results showing the activity of single-agent cetuximab in platinum-refractory SCCHN. It will be interesting to observe if these effects are confirmed in randomized phase III trials in the same patient category.

Disclosure
The author does not have any financial relationships with companies whose products are mentioned in the text.

References


