Current treatments and promising investigations in a multidisciplinary setting

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The care of the patient with squamous cell carcinoma of the head and neck (SCCHN) requires a multidisciplinary approach. For many years, radiotherapy following surgery was considered the standard approach to the treatment of locally advanced resectable disease. Data from randomized trials have confirmed the benefits of concurrent chemotherapy and radiotherapy (chemoradiotherapy) in this setting and this is now the gold standard for treatment. Chemoradiotherapy is also the recommended approach for unresectable disease. Neoadjuvant chemotherapy has been useful in resectable disease where organ preservation is desirable, but a concomitant approach is superior. Although survival benefits have not been consistently demonstrated, the theoretical potential of this approach has lead to continued investigations using newer agents, such as the taxanes. Novel targeted agents, such as antagonists of the epidermal growth factor receptor (EGFR), are showing promise in the treatment of patients with both locally advanced and recurrent/metastatic SCCHN. Treatment issues that require immediate attention include identifying optimal chemoradiotherapy regimens, clarifying the role of neoadjuvant chemotherapy, defining the optimal integration of targeted therapies into combined modality approaches and identifying useful prognostic and predictive factors.

Key words: Cetuximab, chemoradiotherapy, EGFR, neoadjuvant, SCCHN, targeted therapies

Introduction

There are four general presentation categories of advanced stage SCCHN: resectable disease, resectable disease for which organ preserving strategies are desirable, unresectable locally advanced disease, and recurrent/metastatic disease. For many years, standard treatment approaches were: surgery with or without postoperative radiotherapy for resectable disease, radiotherapy for unresectable disease and palliative chemotherapy (with methotrexate or cisplatin in combination with 5-fluorouracil [5-FU] or, more recently, paclitaxel) for recurrent/metastatic disease. However, over the past five years, advances in surgery, radiotherapy and chemotherapy have widened the options for treatment and have improved the prospects for a good outcome following treatment. In this paper, we will discuss the contribution of advances in chemotherapy to current treatment plans and focus on the role of targeted agents, particularly the EGFR inhibitors, in future treatment strategies. For all patients, in view of the complexity of care associated with the management of SCCHN patients, the optimal approach to treatment requires the close cooperation of an experienced multidisciplinary healthcare team (Figure 1) [1], which is responsible not only for the staging of disease, but also the determination of the treatment approaches required to achieve a jointly agreed, well defined goal.

What is the role of chemoradiotherapy in the postoperative setting?

Radiotherapy subsequent to surgery has been a standard approach to the treatment of locally advanced resectable disease. However, the benefits of adding concomitant chemotherapy to radiotherapy in the post-operative setting have recently been confirmed in two randomized trials [2, 3]. In both trials, the rate of local and regional relapse was significantly lower and the disease-free survival longer in patients receiving chemoradiotherapy compared with those receiving radiotherapy alone [2, 3]. In addition, one of the trials reported a significant increase in overall survival ($P = 0.02$), with a 5-year estimated overall survival rate of 53% with chemoradiotherapy and 40% with radiotherapy [3], while the second trial showed a similar trend.

Unresectable disease

The addition of chemotherapy to radiotherapy has now also become the standard approach for unresectable disease [4]. In a phase III trial in 295 patients, the addition of concurrent, high-dose cisplatin to conventional single daily fractionated radiotherapy significantly improved survival compared with radiotherapy alone (3-year projected overall survival 37% vs
Organ preservation and the role of neoadjuvant chemotherapy

The theoretical benefits of neoadjuvant chemotherapy are that it should reduce the tumour burden, eradicate micrometastatic disease and hopefully improve survival. Neoadjuvant chemotherapy also contributes to organ preservation and its utility in this respect has been demonstrated [8, 9]. In a randomized trial in patients with hypopharyngeal cancer, neoadjuvant chemotherapy with cisplatin/5-FU led to improved larynx preservation without any negative effects on survival [9]. Similar findings were made in an earlier trial in laryngeal cancer [8].

The impact of neoadjuvant chemotherapy on survival is controversial. A large meta-analysis failed to confirm statistically significant survival advantages of this approach [7]. However, findings from this meta-analysis should be interpreted with caution, due in part to the heterogeneity of the chemotherapy regimens used in the analysis. The analysis did reveal a benefit for some patients in a subgroup of studies using the combination of cisplatin and 5-FU, as shown in individual randomized trials [10, 11]. Promising results have also been seen in recent studies using taxane-based therapy [12, 13]. In one randomized trial in 358 patients, administration of the combination of docetaxel/platinum/5-FU as neoadjuvant therapy led to significant increases in both progression-free and overall survival [13]. Of particular interest at present is the administration of neoadjuvant chemotherapy prior to chemoradiotherapy. Data from our own trials have suggested high tumour control and cure rates in patients treated with carboplatin (AUC2) and paclitaxel (135 mg/m²) followed by an intensive chemoradiotherapy regimen consisting of paclitaxel, infusional 5-FU and hydroxyurea administered with twice-daily radiotherapy (TFHX) for 5 days of every other week (Figure 2). We recently reported on results of this approach in 69 patients with advanced head and neck disease (mostly stage IV). The 2- and 3-year overall survival rates were 77% and 70% (Figure 3) [14]. At 12 months, five patients were feeding-tube dependent. Currently, this approach is being investigated further in a large multicentre randomized phase III clinical trial. In view of the promising survival data seen in recent studies, the merits of novel neoadjuvant regimens will continue to be investigated prior to radiotherapy alone and chemoradiotherapy.

The role of targeted agents in improving outcome

The introduction of novel targeted agents has provided the promise to more specifically direct anti-cancer treatment to the tumour cells and to reduce the incidence of side effects associated with conventional cytotoxic agents. The range of agents currently being investigated includes anti-angiogenic agents (e.g. vascular endothelial growth factor [VEGF] antagonists), p-53-based therapy, epidermal growth factor receptor (EGFR) inhibitors, immune modulators and cell cycle kinase inhibitors.

The EGFR inhibitors have provided a particularly fertile area of investigation. The EGFR is expressed at high levels in head and neck cancers and high expression is associated with reduced survival [15–17]. A variety of EGFR inhibitors have been investigated in head and neck cancers, and most work to date has been with the tyrosine kinase inhibitors gefitinib [18, 19] and erlotinib [20, 21] and the EGFR-directed IgG1 monoclonal antibody, cetuximab (Erbitux®) [22–25].

Cetuximab demonstrated promising activity in the head and neck setting in in vitro and in vivo studies when combined with cisplatin chemotherapy or radiotherapy [27–31]. In patients, administration of a combination of cetuximab and cisplatin appears to have no effect on the pharmacokinetic profiles of the individual agents [32]. Albanell et al. reported an association between increased tumour activation of mitogen-activated protein kinase (MAPK), which is associated with a relatively high Ki-67 proliferative index, and EGFR expression in SCCHN [33]. In EGFR-dependent models (A431 and DiFi), cetuximab
inhibited MAPK activation at concentrations that inhibited autocrine cell proliferation. The authors suggest that MAPK may be useful surrogate markers of EGFR signalling in clinical studies.

In the clinical setting, cetuximab in combination with cisplatin-based chemotherapy has demonstrated good activity as first-line treatment for recurrent or metastatic SCCHN [22]. In a randomized phase III study, the response rate with cetuximab and cisplatin was 26% compared with 10% for cisplatin and placebo ($P < 0.05$). There was a non-significant increase in overall survival (9.3 vs. 8 months). The addition of cetuximab to combination chemotherapy (cisplatin and 5-fluorouracil) in metastatic and/or recurrent disease also appears promising [23]. In platinum-refractory recurrent and metastatic disease, the activity of cetuximab plus cisplatin or carboplatin was confirmed in two phase II studies [24, 25]. Response rates of 12% and 15%, respectively, and disease control rates of 28% and 54%, respectively, were reported [24, 25]. The activity of single-agent cetuximab in a similar population has also been recently demonstrated, with response rates in the region of those achieved with cetuximab and cisplatin/carboplatin combinations. In locally advanced disease, a phase III study has shown that cetuximab enhances the activity of radiotherapy and improves survival compared with radiotherapy alone [26]. In patients receiving cetuximab plus radiotherapy, the median survival was significantly prolonged by more than two years compared with radiotherapy alone (54 vs 28 months, $P = 0.02$). Notably, in all the studies conducted, cetuximab did not exacerbate the toxicity profiles of co-administered agents. The most common side effects are skin reactions, particularly an acne-like rash, which have become an accepted characteristic side effect of treatment with EGFR inhibitors and which tend to develop in the majority of patients.

Other EGFR-directed MAbs

A number of other EGFR MAbs have been investigated, although these are at an earlier stage of development than cetuximab. The humanized MAb, h-R3, showed pre-clinical activity in the head and neck setting. In A431 SCC cells both in vitro and in vivo, hR-3-induced apoptotic effects of h-R3 were thought to be mediated via anti-angiogenic activity, including an inhibition of the production of the vascular endothelial growth factor [34].
In a phase I dose escalation study, the combination of h-R3 in combination with radiotherapy was investigated in patients with unresectable advanced SCCHN [35]. Seven complete responses were observed among eight evaluable patients. In a phase II study in 24 patients with advanced carcinomas of the head and neck, the combination of h-R3 and RT was well tolerated and appeared to have a positive effect on survival [36]. An interesting observation of treatment with h-R3 is the notable lack of skin reactions reported with this EGFR-directed MAb [36, 37]. These findings are in stark contrast with those reported for other MAbs and TKIs, with which rash is a common finding.

Another anti-EGFR MAb, ICR-62, a rat MAb, was shown to exert direct antiproliferative activity in SCCHN lines and to show additive effects in combination with cisplatin [38]. Subsequent phase I investigation showed that MAb ICR62 can be administered safely to patients with squamous cell carcinomas and that it can localize efficiently to metastases even at relatively low doses [39].

EGFR tyrosine kinase inhibitors

Gefitinib

Gefitinib has demonstrated single-agent activity in patients with recurrent/metastatic disease who had received no more than one prior therapy [18]. Fifty-two patients were enrolled into the study and received gefitinib 500 mg/day. Disease status was reassessed every 4 weeks. Among the 47 patients evaluable for response, there was an overall response rate of 11% and a disease control rate (CR/PR/SD) of 53%, with a median duration of response of 1.6 months. With a median follow-up time of 11.4 months, the median survival was 8.1 months. The main toxicities reported were rash, diarrhoea, nausea and hypercalcaemia. In general, toxicities were mild-to-moderate (grades 1–2). Consistent with the observations for other EGFR inhibitors, there was a link between the development of skin rash and response to treatment: performance status and skin toxicity were strong predictors of response, progression and survival. In a subsequent phase II study, the use of a lower daily dose of gefitinib (250 mg/day) was investigated in a similar patient population [19]. In this study, 43% of the 65 patients enrolled had received chemotherapy for recurrent/metastatic disease. There were only three cases of grade 3/4 toxicity (two diarrhoea and one nausea, all grade 3). However, the tumour response rate appeared to be much lower. Interestingly, pre-treatment plasma VEGF levels were lower in patients with a response or stable disease than in those with progressive disease and did not change after treatment.

The feasibility of using gefitinib combined with the cyclooxygenase 2 (COX-2) inhibitor celecoxib in metastatic and recurrent SCCHN was shown in a small phase I study by Wirth et al. They reported this combination to be well tolerated, the most common side effects being acne-like rash and diarrhoea, with encouraging activity: one-third of the nine evaluable patients achieved a partial response.

The use of gefitinib in unresectable, locally advanced disease is currently under investigation in a phase II study. Patients receive two cycles (8 weeks in total) of neoadjuvant chemotherapy with carboplatin and paclitaxel followed by five 14-day cycles of FHX (days 1–5) in combination with gefitinib (250 mg/day) (Figure 4). After this, patients are scheduled to receive up to 2 years of treatment with gefitinib (250 mg/day) as maintenance therapy. The primary endpoints of this study are locoregional and distant control and survival.

Erlotinib

In a phase II study in 115 heavily pretreated recurrent/metastatic SCCHN patients, the use of single agent erlotinib (at an initial dose of 150 mg daily) was associated with a response rate of 4% and a disease stabilization rate of 38% [20]. The median progression-free and overall survival times were 9.6 weeks and 6 months, respectively. In a similar group of patients, the combination of erlotinib and docetaxel was shown to be active and well tolerated [21].

Other tyrosine kinase inhibitors

Natarajan et al. reported that combining the tyrosine kinase inhibitor EKB-569 with radiation in SCC cells, led to a greater inhibition of cell growth compared with EKB-569 alone [40]. Non-clinical assessment showed that the combination of the tyrosine kinase inhibitor PKI166 with paclitaxel led to significantly longer survival in a model of oral cancer compared with either agent alone, and that this effect was due to an increase in the apoptotic cell fraction [41].

Combinations of EGFR inhibitors with other EGFR inhibitors and with other growth factor inhibitors

Given the importance of the EGFR as an anti-cancer target and the fact that EGFR MAbs and tyrosine kinase inhibitors act at different sites along the signalling pathway, treatment with a combination of these types of EGFR inhibitors may be a viable approach.
strategy. In vivo experiments in A431 tumour xenografts showed that while single-agent gefitinib or cetuximab resulted in transient complete tumour remission only at the highest doses, suboptimal doses of the combination of gefitinib and cetuximab led to the complete and permanent regression of large tumours [42]. Tumour analysis showed superior inhibition of EGFR, MAPK, and Akt phosphorylation, as well as greater inhibition of cell proliferation and vascularization and enhanced apoptosis with the combination compared with single-agent therapy.

Similar findings were reported by Huang et al., with combinations of cetuximab and gefitinib or erlotinib augmenting the inhibition of EGFR phosphorylation in head and neck cancer cell lines over that obtained with single-agent therapy [43]. Again, phosphorylation of downstream effector molecules was enhanced. Flow cytometry and immunoblot analysis revealed an increase in apoptosis induction with dual inhibition. Interestingly, erlotinib and gefitinib were able to inhibit the activation of downstream EGFR signalling effectors in cetuximab-resistant cells.

Both EGFR and VEGF are highly expressed in SCCHN and are associated with a poor outcome. In a phase I study in recurrent/metastatic SCCHN, combined therapy with erlotinib and the VEGF inhibitor bevacizumab was found to be a well tolerated and feasible treatment approach [44]. Efficacy results from this study are awaited.

Conclusions

Developments in the treatment for head and neck cancers over recent years have led to the adoption of a number of new strategies. It is now widely accepted that a multidisciplinary approach to treatment is central to the effective management of disease. In addition, organ preservation has become recognized as an important and desirable goal, wherever feasible. The role of neoadjuvant chemotherapy in organ preservation is now established, but in the absence of confirmed survival benefits, a question mark still hangs over the value of this treatment approach. In the treatment of non-metastatic disease, chemoradiotherapy has emerged as the current standard practice for many clinical treatment settings. We now need to determine the most effective chemoradiotherapy regimens. In both locally advanced and recurrent/metastatic disease, novel investigational agents are showing promise. Results from studies with molecular targeted therapies confirm that these will have an important part to play in the treatment of different stages of head and neck cancers. EGFR inhibitors have shown good utility as radiation sensitizers, in augmenting the effects of cytotoxic chemotherapy and, notably, as monotherapy. The combination of EGFR MAbs and tyrosine kinase inhibitors has shown enhanced activity as has the combination of EGFR inhibitors and other molecular targeted agents. In view of the wealth of possible combinations of agents, it will be necessary to determine those that will yield the best results. The optimal integration of these novel targeted agents into current treatment regimens also needs to be determined.

Disclosure

The author has an affiliation with, or financial interests in, one or more of the corporate organizations involved with products to which this paper refers. The names of the corporate organizations are Lilly, Sanofi, BMS/Imclone, Genentech, OSI, NCI and AstraZeneca. This interest is in the form of grant/research support, consulting, and speaker.

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