CHEMOTHERAPY AND BIOLOGICAL AGENTS IN THE CLINICAL MANAGEMENT OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

Abstract

Historically surgery and subsequently radiotherapy became established as the primary treatments for head and neck squamous cell carcinoma. The significant incidence of recurrence and metastasis in patients with advanced head and neck squamous cell carcinoma treated with surgery or radiotherapy stimulated interest in the potential role of other anti-cancer modalities including chemotherapy. Demonstration of experimental activity with newly discovered drugs in the 1970s led to clinical trials and confirmation of activity in advanced disease, albeit often tempered by significant toxicity. Interest also focused on evaluating a role for chemotherapy in combination with the primary modalities. The goals included reduction in local and systemic relapse, down-staging of the tumour prior to definitive treatment to reduce morbidity of surgery or radiotherapy, organ preservation and biological selection of responders to non-surgical treatment. Considerable effort has been expended trying to identify the optimal agents, administration and schedule of chemotherapy in these different situations. Defining the best combination of the treatment modalities of surgery, radiotherapy and chemotherapy continues to be explored and tailored to the different cancer entities collectively called head and neck squamous cell carcinoma. New agents continue to be tested and the advent of biological therapies, with the potential of molecular based individualised treatment, will impact on the clinical management of head and neck squamous cell carcinoma. Platinum drugs, 5-fluorouracil and taxanes are the most active chemotherapy agents. The anti-epidermal growth factor receptor antibody cetuximab appears effective in Phase III trials.

Chemotherapy for metastatic/recurrent disease

By the early 1970s a number of agents were identified with single agent activity including bleomycin, methotrexate and 5-fluorouracil (5-FU). The discovery of cisplatin brought into practice an agent that has become the cornerstone of chemotherapy for head and neck squamous cell carcinoma (SCC), particularly as its toxicity was ameliorated by improvements in supportive care. Morton and colleagues in 1985 reported one of the few randomised trials comparing chemotherapy with best supportive care for patients with inoperable head and neck SCC unsuitable for radiotherapy.1 High dose cisplatin doubled the median survival from 10 to 20 weeks in comparison to untreated controls, and no benefit was seen from adding bleomycin. Methotrexate alone was popular because of its tolerability and proven responses, however combination with cisplatin resulted in increased toxicity but no improvement in response.2 The administration of 5-FU by four to five day continuous venous infusion appeared to be an effective radiation sensitisert and also to have a good response rate used alone.4 The combination of cisplatin with infusional 5-FU was shown to be significantly more active than with bolus 5-FU.5 Jacobs et al in 1992 showed benefit from the combination of cisplatin with 5-FU over those drugs as single agents.6 By this time in the early 1990s the less toxic cisplatin analogue carboplatin had become available and was being used in place of cisplatin in many tumour types. A landmark randomised trial compared the combinations of cisplatin/5-FU versus carboplatin/5-FU versus methotrexate (see table 1) in chemotherapy naïve patients with inoperable recurrent or metastatic disease.7 Predictably greater toxicity was observed with the combinations, particularly cisplatin/5-FU. Response rates were higher with the combinations but overall survival was no different. In practice this has led clinicians to consider combination therapy in the following two patient groups: those where a response in symptomatic recurrence would be of palliative benefit; and physiologically fit patients who are prepared for the greater inconvenience, particularly of multi-day 5-FU infusion. For patients with reduced performance, weekly methotrexate retains a role. The advent of the taxanes in the 1990s and demonstration of their activity in Phase II trials has added a new class of agent to the management of cases of recurrent or metastatic head and neck SCC, however the same issues of toxicity and absolute benefit pertain. Phase II trials have reported response rates for paclitaxel over three hours of 20%8 and of 40% for a 24-hour infusion, with a median survival time (MST) of 38 weeks.9 For Docetaxel the reported response rate and MST are 21-42% and 27-35 weeks.10,11 Given the activity of taxanes, non-platinum doublets have been tested with the goal of avoiding cisplatin toxicity by combining taxane with five day infusional 5-FU. One of the largest Phase II studies used Docetaxel and infused 5-FU with a response rate of 21% but still had considerable toxicity.12 Paclitaxel combined with cisplatin demonstrated a response rate of 35%, but was limited by severe neutropenia.13 Paclitaxel with carboplatin showed better tolerability although neutropenia was still
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significant and a response rate of 27% with MST of 4.9 months. A randomised trial of cisplatin/FU versus cisplatin/paclitaxel showed equivalence between the treatments with identical response rates (27% and 26%) and MST (8.1 and 8.7 months).

The value of triplet combinations (platinum + 5-fluorouracil + taxane) has been examined in Phase II trials. A response rate of 44% has been reported for docetaxel/cisplatin/FU. Paclitaxel has been used in combination with either cisplatin or carboplatin and ifosfamide with response rates of almost 60%, but with severe neutropenia. The advent of light-weight ambulatory infusional devices has improved the convenience of 5-FU treatment. The 5-FU component has also been met by oral analogues including capecitabine, which can provide prolonged systemic exposure equivalent to intravenous infusion; a Phase II trial reported similar response rate and survival to the classic cisplatin/5-FU doublet. It does have the potential disadvantage of requiring oral or enteral administration, which may not be feasible in locally recurrent head and neck SCC. Other agents with some reported activity include ifosfamide, gemcitabine, irinotecan, (reviewed in Murphy) and pemetrexed. Other chemotherapy approaches have included intra-arterial administration and direct injection into local recurrences. In the palliative setting reducing toxicity and inconvenience from treatment is a relevant aim. Earlier trials focused particularly on response rates, whereas more recent studies have also paid attention to the effects of treatment on quality of life.

**Induction chemotherapy**

Although not a curative modality the question was addressed as to whether addition of systemic chemotherapy could improve the local and distant failure rates when combined with definitive local surgery or radiotherapy. Such an approach was considered safe given the high response rates in pilot studies of treatment naïve patients. By using chemotherapy as the initial modality it was hoped local treatment could be reduced in extent, thus reducing toxicity and permitting preservation of functional aerodigestive organs. A further proposition was that tumour

<table>
<thead>
<tr>
<th>Study population</th>
<th>Treatment arms</th>
<th>Outcome (RR, LRC, MST, OS)</th>
<th>p value</th>
<th>Year (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent and metastatic head and neck SCC</td>
<td>Cisplatin 100mg/m2 D1 5-FU 1g/m2 D1-4 q3w, Carboplatin 300mg/m2 D1 5-FU 1g/m2 D1-4 q4w, Methotrexate 40mg/m2 weekly</td>
<td>RR 32%, MST 6.6m, RR 21%, MST 5.0m, RR 10%, MST 5.6m</td>
<td>P&lt;0.001 for RR</td>
<td>1992</td>
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<tr>
<td>Stage III&amp;IV resectable laryngeal ca</td>
<td>Cisplatin 100mg/m2 D1 5-FU 1g/m2 D1-5 q3w then RT (laryngectomy if no response or recurrence), Laryngectomy then RT</td>
<td>5 yr overall survival (OS) 42%, 64% larynx preservation, 5 yr OS 46%</td>
<td>Not significant (NS) for OS</td>
<td>1991</td>
</tr>
<tr>
<td>Unresectable head and neck SCC</td>
<td>RT 70Gy, RT 70Gy with Cisplatin 100mg/m2 D1,22,43, RT 70Gy, Cisplatin 75mg/m2 D1, 5-FU D1-4 x2, then RT 30-40Gy, Cisplatin 75mg/m2 D1,5-FU d1-4 x1</td>
<td>3yr OS 23%, MST 12.6m, 3yr OS 37% MST 19.1m, 3yr OS 27% MST 13.8m</td>
<td>p&lt;0.014</td>
<td>2003</td>
</tr>
<tr>
<td>Stage III&amp;IV resectable laryngeal ca</td>
<td>Cisplatin 100mg/m2 D1 5-FU 1g/m2 D1-5 q3w then RT RT 70Gy with Cisplatin 100mg/m2 D1,22,43</td>
<td>2yr intact larynx 75%, 2yr intact larynx 88%, 2yr intact larynx 70%, OS no difference</td>
<td>p&lt;0.005</td>
<td>2003</td>
</tr>
<tr>
<td>Stage III/IV oropharynx</td>
<td>RT 70Gy, RT 70Gy with Carboplatin 70mg/m2/day, 5-FU 600mg/m2/day both D1-4 commencing D1,22,43</td>
<td>5yr OS 16%, LRC 25%, 5yr OS 22%, LRC 48%</td>
<td>p=0.002 for LRC, p=0.05 for OS</td>
<td>2004</td>
</tr>
<tr>
<td>High risk resected head and neck SCC</td>
<td>RT 60-66Gy, RT 60-66Gy with Cisplatin 100mg/m2 D1,22,43</td>
<td>2yr LRC 72%, 2yr LRC 82%, OS no difference</td>
<td>p=0.01</td>
<td>2004</td>
</tr>
<tr>
<td>High risk resected head and neck SCC</td>
<td>RT 66Gy, RT 66Gy with Cisplatin 100mg/m2 D1,22,43</td>
<td>5yr LRC 69% OS 40%, 5yr LRC 82% OS 53%</td>
<td>p=0.007 for LRC, p=0.02 for OS</td>
<td>2004</td>
</tr>
<tr>
<td>Stage III/IV head and neck SCC</td>
<td>RT (various regimens) RT with cetuximab 400mg/m2 w1 then 250mg/m2/week</td>
<td>MST 29.3m, MST 49m</td>
<td>P=0.03</td>
<td>2006</td>
</tr>
</tbody>
</table>

Abbreviations: RR response rate, LRC loco-regional control rate, MST median survival time, OS overall survival, EGFR epidermal growth factor receptor, NS not significant.
response to chemotherapy could help select patients with aggressive disease who could be fast-tracked to surgical salvage. An important historical study of induction chemotherapy came from its examination in laryngeal carcinoma as a component of a voice preserving approach. The landmark Veterans Affairs study in 1991 showed induction chemotherapy followed by radiotherapy could preserve the larynx in 64% of patients with a similar two-year survival rate. Surgical salvage was available to patients on the non-surgical arm who experienced local recurrence. A subsequent trial randomising patients with laryngeal cancer planned to receive definitive radiotherapy to induction versus concurrent chemotherapy has provided evidence in favour of the concurrent approach. Although less popular outside of North America, the use of induction chemotherapy has been re-examined using newer agents such as the taxanes with promising activity. A new generation of clinical trials have looked at combining induction therapy with concurrent radiotherapy, utilising several active chemotherapy agents with the hope of reducing the risk of both local and distant recurrences. Induction chemotherapy has been associated with reduced risk of metastases, whereas concurrent chemo-radiotherapy has been particularly associated with a reduction in loco-regional relapse, hence the rationale for combining the two approaches. Hitt et al reported an advantage for induction with cisplatin, 5-FU and paclitaxel followed by cisplatin chemoradiotherapy over induction with cisplatin and 5-FU alone, with improved disease free survival and borderline significant overall survival benefit. A recent report in abstract form has suggested adding Docetaxel to cisplatin and 5-FU induction therapy for resectable laryngeal cancer improves the laryngeal preservation rate.

Concurrent chemo-radiotherapy as definitive treatment

The development of concurrent chemo-radiotherapy for advanced head and neck SCC began soon after the discovery of chemotherapy activity in head and neck SCC, with testing of the combination of chemotherapy with radiotherapy as treatment for patients considered unsuitable for surgery. A Medline search from 1975 identifies at least 40 randomised studies comparing radiotherapy with or without concurrent chemotherapy. These studies tested different schedules of radiotherapy (such as hyperfractionated, accelerated or split course) and used various chemotherapy agents, initially bleomycin, methotrexate and 5-FU, with most recent studies using platinum drugs. Two formal meta-analyses have confirmed a benefit with chemotherapy, in particular with platinum drugs. Two large randomised trials have provided evidence for the use of either cisplatin or carboplatin with 5-fluorouracil in combination with radiotherapy as being superior to the use of radiotherapy alone. Denis et al showed improved loco-regional control and overall survival in advanced oropharyngeal SCC treated with concurrent carboplatin and 5-FU. Adelstein et al in a three way study compared radiotherapy, split course chemoradiotherapy using cisplatin and 5-FU and concurrent chemo-radiotherapy using high dose cisplatin. Patients in the split course arm were able to undergo interval surgery if a sufficient response was achieved. At three years a survival advantage was shown for the group receiving concurrent treatment compared with both other arms which were not different from one another. This trial reduced ongoing interest in split course approaches.

Unresolved issues include preference for cisplatin over carboplatin, scheduling of platinum (as daily, weekly and three weekly administration have all been investigated) and preference for single agent or combinations (eg. with 5-FU or taxane). Overall however, some concurrent platinum chemotherapy appears better than no chemotherapy and major improvements are likely to come from additional novel agents rather than further manipulating platinum administration.

Post-operative concurrent chemo-radiotherapy for high risk patients

Two large multi-centre randomised trials have confirmed improved two year loco-regional control, and in a study with longer follow-up improved estimated five-year survival, following the addition of high dose three weekly cisplatin to patients receiving radiotherapy for high risk (node positive with extracapsular spread, microscopic positive margins or lymphvascular invasion by tumour cells) resected mucosal head and neck SCC. Details of the trials are shown in Table 1.

Novel biological agents

As in other solid malignancies interest in immune therapies led to the testing of immune modulating agents, especially interferon, in combination with chemotherapy treatment of advanced head and neck SCC, however such trials failed to show a benefit. More recently, an understanding of the molecular abnormalities underlying head and neck SCC has led to development of specific biological therapies targeting those alterations. The agents of specific interest are the p53 oncolytic virus, tyrosine kinase inhibitors (TKI), anti-angiogenic agents and the anti-epidermal growth factor receptor (EGFR) antibody cetuximab. The oncolytic p53 virus, capable of infecting and destroying tumour cells but not normal cells, captivated the attention of cancer researchers and clinicians by demonstrating that a tumour specific molecular defect could be used to selectively target tumour cells and achieve an appreciable clinical anti-tumour effect. A related important observation was the “bystander killing” whereby tumour cells not directly infected underwent cell death, presumably subsequent either to signalling from infected cells or due to release of material from dying cells. Ultimately this therapeutic approach has not been able to achieve sufficient systemic delivery to be a useful treatment. Anti-angiogenic agents have been tested in Phase I/II studies in combination with chemotherapy and TKI.

The EGFR receptor is over-expressed in up to 80% of head and neck SCC and some degree of expression can be detected by immunohistochemistry in almost all
cases. The EGFR receptor belongs to a family of cell surface receptors whose members dimerise following binding of a specific ligand, leading to activation and subsequent intracellular signalling. As the receptor family members can bind in a variety of combinations the system has a range of modulated responses to stimuli. In certain cases receptors or down-stream effector molecules may acquire autonomous activation and can thus lead to an over-active pathway in the absence of over-expression. Two major intracellular pathways are activated by EGFR stimulation. The mitogen activated protein kinase pathway leads ultimately to changes in DNA transcription that promote cell growth and division. The other major pathway is downstream of the Akt protein, which leads to apoptosis resistance. Dysregulation of the EGFR signalling pathway can thus primarily lead to cells acquiring most of the important features of the malignant phenotype. Downstream EGFR activation has been targeted using the TKIs erlotinib and gefitinib, however low response rates were observed.40,41 Understanding the molecular predictors for clinical response is an area of intense research interest.42 The EGFR receptor can also be disrupted by the monoclonal antibody cetuximab. The value of cetuximab in combination with radiotherapy has been confirmed in a randomised Phase III trial with improved loco-regional control and overall survival in patients with locally advanced tumours. Interestingly, a post-hoc subset analysis suggested the benefit may be dependant on the radiotherapy schedule.43 Cetuximab has also been used with cisplatin in a Phase III study in advanced disease, showing a modest improvement in response rate and a survival advantage in patients developing rash.44 It is being tested in a variety of other settings.

Trials in progress and future directions

Achieving the best outcomes for the lowest morbidity is a major goal of clinical research in head and neck SCC. Acute side effects of chemo-radiotherapy can be severe, distressing and potentially fatal. Management of such patients requires well-resourced units with experienced medical, nursing and allied health staff. The long-term morbidity of chemo-radiotherapy approaches is becoming increasingly recognised, partly because of the benefit of these treatments in extending duration of disease control. Reduction of acute mucosal toxicity by using keratinocyte growth factor is being explored.45 The ongoing improvements in radiotherapy techniques are also likely to further ameliorate toxicity. For relapsed or metastatic disease the important recent advances in understanding head and neck SCC tumour biology and identification of molecules to reverse these abnormalities should lead to new therapies entering clinical trial. Rather than providing magic bullets these agents are likely to be most efficacious in combination with fellow agents, conventional therapies such as radiotherapy or chemotherapy and in subgroups of patients who can be identified as harbouring specific molecular derangements driving the malignant phenotype.

In summary, the last few years have seen significant advances in the management of the heterogeneous cancers collectively known as head and neck SCC. Modest but definite improvements in survival with organ sparing have been achieved, but at the cost of more severe acute and perhaps also long-term toxicities. Defining the optimum use of existing agents has been a significant step that has required collaboration between the different specialities involved in the care of primary head and neck SCC patients and the endurance of patients to participate in trials and undergo toxic therapies. The advent of new chemotherapeutic agents and ongoing studies to identify the best combination, sequence and timing with radiotherapy will continue to improve outcomes. Most excitingly the advent of effective biological therapies promises translation of our increasing knowledge of the molecular pathology of head and neck SCC into more cures or equally effective but less toxic treatments.

Disclosure: The author has participated in an advisory board for Merck AG, manufacturers of Erbitux.