Chemotherapy for symptom control in recurrent squamous cell carcinoma of
the head and neck

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Summary

Background: The role of chemotherapy in patients with recurrent squamous cell carcinomas of the head and neck (SCCHN) is unclear. The aim of this study was to assess the ability of combination chemotherapy to control symptoms in this setting.

Patients and methods: Using a prospectively accrued database all patients referred for chemotherapy with symptomatic relapse following surgery were identified. Objective response was recorded using standard criteria and maximum symptom response was assessed retrospectively from case notes using a published scoring scale.

Results: A total of 57 (median age 56, range 37–85) patients were studied who had received mainly cisplatin/5-fluorouracil combinations. Thirty-seven had previously received radiotherapy. Fifty-two patients had evaluable disease; 18 (35%) had objective responses (14 PRs and 4 CRs). There were a total of 103 symptoms recorded with eight different individual symptoms. Forty-four (43%) symptoms improved on treatment, 52 (50%) were unchanged and 7 (7%) worsened. The number of patients with improvement in the most frequently recorded symptoms were as follows: pain 11/28 (39%), swelling 12/23 (52%) and dysphagia 6/18 (33%). Sixty-seven percent of patients with objective response also had an improvement in their symptoms but a significant proportion (33%) of non-responders had a symptomatic response. Lack of objective response was not correlated with worsening symptoms. Grade 3/4 toxicity was uncommon (6–17%) and there were no toxic deaths. A majority of patients (82%) experienced either no change or an improvement in performance status.

Conclusion: These results demonstrate that chemotherapy improves many of the symptoms associated with recurrent SCCHN, without deterioration in performance status. Symptomatic improvement is more likely if there is evidence of significant tumour shrinkage, but even non-responding patients can benefit.

Key words: chemotherapy, head and neck cancer, symptom control

Introduction

Squamous cell carcinoma is the commonest histological sub-type of tumour occurring in the head and neck region, with the principal sites of involvement being oral cavity and larynx [1]. In spite of progress in surgical and radiotherapeutic techniques, the prognosis of patients with this diagnosis is poor; only 30% are alive at five years and not all will be disease-free [2]. The role of chemotherapy in the management of SCCHN is not yet fully defined. Primary (neoadjuvant) treatment with chemotherapy is associated with high response rates and preservation of organ function but has not been shown to influence survival [3–6]. Similarly, adjuvant chemotherapy has at best marginal benefit [7–9].

In the setting of advanced or recurrent disease, chemotherapy is given with palliative intent as the reported median survival is generally poor, 6–10 months [10, 11]. However, many patients (up to 75%) have complete disappearance or good improvement in at least one of their tumour-related symptoms and patients experiencing an improvement in quality of life and/or an objective response have increased survival [12, 13]. Improvement in symptoms and function is not confined to chemotherapy but also occurs with clinical responses to locally administered interleukin-2 [14, 15].

Chemotherapy has been reported to give significant palliation and improvement in overall quality of life in patients with other solid tumours, e.g., non-small-cell lung cancer (NSCLC), pancreatic cancer etc. [16–20]. The study by Hardy et al. [20] demonstrated that patients with NSCLC can have an improvement in their symptoms without an objective response to chemotherapy. Of 24 symptomatic patients treated with a well tolerated chemotherapy regimen only 21% had an objective response but 75% reported a complete disappearance or good improvement in at least one of their tumour-related symptoms. In a later publication from the same group, only 32% of assessable patients achieved an objective response but 69% of patients had a complete disappearance or substantial improvement in their tumour related symptoms [17].

Many patients with recurrent SCCHN have distressing symptoms which are difficult to control by non-
cytotoxic agents and we therefore set out to assess in our patients to what extent chemotherapy resulted in symptomatic improvement. We also aimed to determine if there was a correlation between objective and subjective response.

Patients and methods

All patients referred to the Royal Marsden Hospital Head and Neck Unit for palliative chemotherapy for symptomatic recurrent SCCHN between 1989 and 1995 were considered for this study. The majority of patients were entered into prospective studies and histological confirmation of the diagnosis was obtained for all cases. Prior to treatment the following investigations were performed: physical examination, full blood count (FBC) and differential, liver function tests (LFTs), serum calcium and electrolyte concentrations, measurement of renal function using $\text{Cr} \text{EDTA}$ clearance, chest X-ray (CXR), liver ultrasound and computerised tomography (CT) scans of disease sites in the head and neck. Patients were required to have an ECOG performance status of $\leq 3$, total white cell count $> 3 \times 10^9$ ml, platelet count $> 100 \times 10^9$ ml, normal serum creatinine and glomerular filtration rate (GFR) $> 60$ ml per minute. Patients with significant general medical problems, recent uncontrolled cardiac failure, sepsis, etc., cerebral metastases or prior invasive malignancy were excluded.

Four regimens were used: single agent methotrexate, cisplatin/5-fluorouracil (5-FU) with and without interferon (IFN), and cisplatin/epirubicin/bleomycin. Appropriate dose adjustments were made for grade 2–4 toxicities and carboplatin was substituted for cisplatin if the GFR fell below 60 ml/min or grade 3/4 neurotoxicity was encountered.

Tumour responses were measured according to standard WHO criteria [21]. Responses were assessed by CT, CXR or ultrasound as appropriate, and repeated every two cycles and at one month after the last treatment cycle. Response was defined as objective (OR) if there was a partial (PR) or complete remission (CR) and subjective or symptomatic (SR) where, irrespective of the change in size of the tumour, the patient reported an improvement in their symptom(s). Toxicity was graded according to the Common Toxicity Criteria [22].

CR was defined as a complete disappearance of all clinical, radiological and biochemical evidence of disease for at least one month and OR as a reduction in the product of two perpendicular diameters of measurable disease by at least 50% for the same period of time. Patients who demonstrated a reduction in their disease of 25%–49% were said to have a minor response (MR). Separate response rates for the primary and metastases were determined. Increase in tumour size of more than 25% defined progressive disease (PD) and all other responses were ascribed as no change (NC).

Individual symptoms were documented prior to each cycle and one month after the last treatment. They were recorded as being either a) worse b) unchanged c) improved or d) resolved. A subjective response in a particular symptom was defined as c) or d). Overall symptomatic control was evaluated for each patient and if multiple symptoms responded differentially then the results were interpreted as follows: no change + worse scored worse; no change + better scored better and ‘better + worse’ and ‘no change’ scored no change [20, 23]. This data was extracted retrospectively from patients' case-notes. Analgesics were prescribed as required, but a reduction in analgesic consumption was taken as evidence of improvement in pain control. Administration of other drugs for symptom control e.g., corticosteroids did not preclude the patients from the study, especially as many of them were referred precisely because their symptoms could not be controlled by non-cytotoxic means.

Patients were assessed before each cycle for any change in performance status and the following investigations were performed: FBC, LFTs, serum calcium and electrolyte concentrations. Appropriate imaging was performed on alternate courses unless there was clinical evidence of PD. Renal function, as measured by $\text{Cr} \text{EDTA}$ clearance was repeated after three courses unless otherwise indicated.

Time to progression was measured from start of treatment to date of disease progression; survival and progression-free survival were examined using the Kaplan–Meier product-limit method [24]. The Mann–Whitney test was used to determine whether or not performance status was a significant factor for improved survival among responders and non-responders, along with the log-rank analysis which was used to determine if the median survival of objective responders was significantly better than that for non-responders [25].

Results

Fifty-seven patients (38 male, 19 female) were identified who had received at least one course of chemotherapy. The median age was 56 years (range 37–85) and median WHO performance status was 1. All patients had prior surgery, 37 had previously received radiotherapy. The primary sites of disease were as follows: oral cavity ($n = 19$), cervical lymph nodes with no primary (14), larynx (9), oropharynx (7), hypopharynx (5), nasopharynx (1), paranasal sinus (1), and submandibular gland (1). Table 1 summarises the patient characteristics by chemotherapy regimen.

Five patients were non-evaluable because they were lost to follow-up and did not have their symptoms assessed adequately post-treatment. Of the remaining 52 patients, 18 (35%) had an objective response (14 PRs and 4 CRs). Objective response among patients with local and metastatic disease was 33% (15/45) and 43% (3/7), respectively (Table 2). Minor response was observed in 16 patients (30%), 15/45 with local disease and 1/7 with distant metastases. Table 3 shows the objective response rate according to the regimen administered.

A total of 103 symptoms were reported within eight different symptom categories. Forty-four (43%) of the symptoms improved with treatment, 52 (50%) were un-

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>CIS/5-FU</th>
<th>CIS/5-FU + IFN</th>
<th>Other*</th>
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<tbody>
<tr>
<td>No patients</td>
<td>43</td>
<td>6</td>
<td>8</td>
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<tr>
<td>Median age</td>
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<td>56</td>
<td>56</td>
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<tr>
<td>Range</td>
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<td>39–85</td>
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<td>Distribution of disease sites at relapse</td>
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<tr>
<td>Local recurrence</td>
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<td></td>
<td></td>
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<tr>
<td>Nodal</td>
<td>18</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>18</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Larynx</td>
<td>4</td>
<td>–</td>
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<tr>
<td>Oropharynx</td>
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<td>–</td>
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<tr>
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<td>2</td>
<td>–</td>
<td>1</td>
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<tr>
<td>Hypopharynx</td>
<td>2</td>
<td>–</td>
<td>1</td>
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<tr>
<td>Paranasal sinus</td>
<td>1</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Nasopharynx</td>
<td>1</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Submandibular glands</td>
<td>–</td>
<td>1</td>
<td>–</td>
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<tr>
<td>Metastatic recurrence</td>
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<tr>
<td>Lung</td>
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<td>–</td>
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<tr>
<td>Liver</td>
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<td>1</td>
<td>–</td>
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<tr>
<td>Skin</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Patients evaluable for response</td>
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<tr>
<td>Mean no. of courses</td>
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<td>1.9</td>
</tr>
</tbody>
</table>

* Methotrexate and bleomycin + epirubicin + cisplatin.
changed and 7 (7%) worsened. The numbers of patients with improvement in the most frequently reported symptoms were as follows: pain 11/28 (39%), swelling 12/23 (52%) and dysphagia 6/18 (33%) (Table 4).

Twelve out of the 18 patients (67%) who had an objective response to treatment also had a symptomatic response, including three patients that had a complete resolution of their symptoms. None of these patients had a worsening of their symptoms although 6 (33%) experienced no change (Table 5). Half of the patients who had an MR experienced an improvement in their symptoms, 2 (13%) of whom had a complete symptomatic response, 2 (13%) a deterioration and 6 (46%) patients no change. Six patients (33%) whose disease either failed to respond to chemotherapy or whose tumours progressed through treatment reported symptomatic improvement, with one reporting complete resolution of their symptoms. None of these patients who failed to respond to chemotherapy gained 5-FU ± IFN. These studies have shown that serious toxicity (WHO grade 3/4) is uncommon: nausea and vomiting 17%, mucositis 8%, and sepsis 6% [24-26]. The likelihood of experiencing grade 3/4 toxicity was higher in patients who received IFN.

The median disease-free survival for all patients was 152 days (range 19–1951). The median survival for patients who had an objective response was 365 days (50–3843) and 164 days (6–408) for non-responders. The five-year survival was 11% for responders and 7% for non-responders (Figure 1).

### Discussion

The main aim of this study was to quantify the ability of chemotherapy to relieve symptoms and to correlate this with objective response. The data presented demonstrate that palliative chemotherapy has the potential to improve many of the symptoms associated with SCCHN. Of 52 evaluable patients, 35% had an objective response, whilst 50% reported complete disappearance or improvement in at least one of their tumour-related symptoms, and only 7% worsened during chemotherapy. All categories of symptoms were improved and 33% of patients who failed to respond to chemotherapy gained...
benefit. This demonstrates that symptom response in SCCHN can occur independently from objective response, a phenomenon observed with other tumours [17]. Symptom response followed objective response in 67% of patients and this is consistent with other studies [29]. A correlation was also found between response and an improvement in WHO performance status. This needs to be balanced against the experience of others who have shown that some patients may experience a temporary reduction in quality of life because of side effects due to treatment [7].

The median survival for patients who responded was longer than for non-responders; 365 days (range 50–3843) compared to 164 days (6–408). However, the five-year survival rate was not significantly different between responders and non-responders, which is consistent with previously reported studies [2, 6, 7, 30]. The low rate of long term survival reinforces the view that chemotherapy for relapsed SCCHN should be regarded as an essentially palliative treatment.

Patients with advanced head and neck cancer who are symptomatic present a difficult challenge to clinicians. Many have a history of heavy smoking and alcohol intake, and have poor nutrition which is often exacerbated by their disease and treatment. Similarly, symptoms such as difficulty in swallowing, dysphagia and pain can be multifactorial in origin, resulting from the original surgery and radiotherapy as well as disease recurrence. Furthermore, formal quality of life assessments and symptom scores in this group of patients can be difficult to evaluate because of communication difficulties and other general medical problems.

Chemotherapy remains non-curative for advanced or recurrent SCCHN, but we have shown significant palliation in this group of patients treated by chemotherapy. In addition, the improvement in performance status and manageable toxicity implies overall benefit in terms of quality of life and emphasises the value of using symptom control as an endpoint in trials of chemotherapy for this tumour type. On this basis, we suggest that future studies in recurrent SCCHN should place as much emphasis on recording data on symptom control as on measuring objective responses and survival.

References

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