Current chemotherapies for recurrent/metastatic head and neck cancer

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Surgery and radiotherapy are generally not an option for recurrent/metastatic head and neck squamous cell carcinoma. Chemotherapy is the only possible treatment. The five major drugs active in monotherapy are methotrexate, cisplatin, 5-fluorouracil (5-FU), cetuximab (an antiepidermal growth factor receptor antibody) and taxanes (paclitaxel or docetaxel). They allow 10–25% response with a median survival of approximately 6–8 months. Various chemotherapy doublets may achieve higher response rates, up to 45–50%, but overall survival remains unchanged. As recurrent patients are often symptomatic, better response is associated with better quality of life and the standard treatment for patients with performance status 0–1 is the combination of cisplatin and 5-FU. Recently, the triplet cisplatin-5-FU-cetuximab, which has been shown to result in an increased response rate and a significantly better median survival of 10.4 months, has become the new treatment standard. *Anti-Cancer Drugs* 22:621–625 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2011, **22**:621–625

Keywords: cetuximab, cisplatin, docetaxel, epidermal growth factor receptor, 5-fluorouracil, methotrexate, paclitaxel, recurrent/metastatic, squamous cell carcinoma

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Received 30 October 2010 **Revised form accepted** 31 October 2010

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for 5% of all newly diagnosed cancers in adults in the USA and 8% of cancers worldwide [1]. Two thirds of patients present with locally advanced disease and 10% are metastatic [2]. Despite aggressive and optimal plurimodality treatment with surgery, radiotherapy and chemotherapy, approximately 33 to 50% of patients in Western countries relapse. In these cases, surgery and radiotherapy are no longer possible and the only treatment option is chemotherapy. The chemotherapeutic drugs active in HNSCC are methotrexate, cisplatin, 5-fluorouracil (5-FU), taxanes and cetuximab. Methotrexate monotherapy has long been the standard treatment for these patients, with fewer responses than cisplatin-based chemotherapy but with similar overall survival. However, relapsing patients often have a local recurrence and symptoms such as trouble in swallowing, eating and speaking; higher objective response could make a positive difference to them by improving their quality of life. Recently, a combination of three drugs, cisplatin, 5-FU and cetuximab, has been shown to result in increased overall survival. This review will summarize available chemotherapies for recurrent/metastatic HNSCC.

Monotherapy (Table 1)

Methotrexate

Historically, methotrexate was the first drug used for patients with HNSCC. Two randomized phase III studies have reported response rates from 10 to 16% at the dose of 40 mg/m^2 [3,4]. Tolerance is globally satisfactory with only 10% leucopenia or grade 3–4 mucositis, but overall survival is poor: 5.6 and 6 months, respectively. An increase in doses with detoxification by leucovorin has allowed obtaining of 76% of responses in a small trial but has been associated with important toxicity and toxic deaths [13]. However, randomized trials have not shown any difference in overall survival despite high toxicity [14–17]. Leucovorin, which decreases the toxicity of high-dose methotrexate, could also limit its efficiency [17]. The standard dose thus remains 40 mg/m^2/week.

Cisplatin

At the end of the 1970s, two studies showed the efficacy of cisplatin in HNSCC, with high rates of response from 25% in pretreated patients to 70% in others [18,19]. A randomized four-arm trial comparing cisplatin, bleomycin, the combination of both drugs and best supportive care confirmed the 25% response rate for cisplatin, associated with a significant 10-week increase in survival. Bleomycin is deleterious in these patients, whereas cisplatin, at a dose of 50 mg/m^2 every 15 days, has been shown to induce 15% objective responses [20]. At 100 mg/m^2 every 28 days, two phase III trials have shown responses from 10 to 17% and an overall survival between 5.7 and 8 months, but at the expense of a certain toxicity [5,6]. Indeed, many grade 3–4 toxicities, including 14% patients with neutropenia, 10% with dehydration, 18% with nausea and vomiting, 14% with asthenia, 11% with anaemia and 10% with infections, have been reported.

0959-4973 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e3283421f7c

Table 1 Monotherapy for recurrent/metastatic head and neck squamous cell carcinoma (phase III trials, unless otherwise specified)

Chemotherapy regimen	Response (%)	Overall survival (months)	References
Methotrexate (40 mg/m^2/week)	10–16	5.6–6	[3,4]
Cisplatin (100 mg/m^2/3 weeks)	10–17	5.7–8	[5,6]
5-FU (1000 mg/m^2/d, 5 days/3 weeks)	13		[6]
Paclitaxel (80 mg/m^2/week)	43	8.5	[7] phase II
Docetaxel (35 mg/m^2/week)	6–42	6–11.3	[8–10] phase II, [11]
Cetuximab (400 mg/m^2 then 250 mg/m^2/week)	13		[12]

5-FU, 5-fluorouracil.

5-fluorouracil

5-FU is an antimetabolite with better efficacy when used in continuous infusion. In monotherapy at the dose of 1000 mg/m^2/day during four consecutive days, repeated every 21 days, it has led to 13% responses, with 13% patients developing mucositis and 11% grade 3–4 anaemia [6].

Paclitaxel and docetaxel

Taxanes are the most recently developed chemotherapy drugs for HNSCC treatment. Paclitaxel has been used according to multiple schedules. The 96-h infusion schedule had yielded disappointing results [21]. A study of 34 patients undergoing 24-h infusion of 250 mg/m^2 paclitaxel has shown 40% responses with a median survival of 9.2 months [22]. However, treatment toxicity was severe with 91% neutropenia and two toxic deaths by myocardial infarction and febrile neutropenia. As in breast cancers, weekly administration of paclitaxel seems to be more efficient and is much better tolerated. A study of 60 patients treated with 80 mg/m^2/week has shown response rates of 43% with an overall survival of 8.5 months [7].

Docetaxel is also effective in monotherapy in patients with recurrent HNSCC. At the dose of 100 mg/m^2 every 3 weeks, response rates vary between 32 and 42% [23,24], but with 69% asthenia, 61% neutropenia, 45% cutaneous toxicity, 31% peripheral oedema in the first study, and 53% fever in the second. As for paclitaxel, weekly administration schedules have been developed: the response rates remained high, from 25 to 42%, with a median overall survival between 6 and 11.3 months [8–10].

It is important to underline that all the studies investigating taxanes in monotherapy were phase II trials whose results are more likely to be favourable. A phase III trial of taxane monotherapy in cisplatin-resistant patients has shown that docetaxel was associated with only 6% responses and an overall survival of 6 months [11].

Cetuximab

Progress in molecular biology has led to a better understanding of the mechanisms of cancer and of its biological pathways. The epidermal growth factor receptor (EGFR) is expressed by 90% of HNSCC, and its expression is correlated with unfavourable prognosis [25]. EGFR activation stimulates cellular proliferation, the formation of metastases and neoangiogenesis, and confers resistance to apoptosis.

Cetuximab, an anti-EGFR monoclonal antibody, blocks EGFR phosphorylation and thus, its activation [26]. It probably also acts by stimulating the immune system through the induction of antibody-dependent cell cytolysis: the constant part of the antibody is bound by specific receptors to the macrophages, which then eliminate the cancer cells [27,28]. In monotherapy, weekly administration of cetuximab (400 mg/m^2 on the first week and 250 mg/m^2/week thereafter) after failure of various chemotherapies has produced response rates of 13% and a control of the disease in 46% of cases [12]. The most common toxicities were diarrhoea and acne-like reactions; and 49% of the patients had cutaneous toxicity, essentially of grade 1–2 (only 1% grade 3–4). Diarrhoea prophylaxis and prescription of moisturizing creams and cyclines are recommended.

Other oral EGFR inhibitors such as erlotinib, gefitinib and lapatinib have been tested but have yielded disappointing results [29–32].

Combination of chemotherapies (Table 2)

The aim of combining drugs that have been found to be efficient in monotherapy is to increase the rate of response and overall survival. Before going into the details of the various associations available, most of them cisplatin-based, it is important to recall that HNSCC patients are often symptomatic with pain or with language, breathing or feeding disorders, and that any treatment increasing response rates, although not overall survival, remains interesting by improving the patient's quality of life.

Cisplatin and 5-fluorouracil

The combination of cisplatin and 5-FU was first tested in the early 1980s and has become the standard treatment for patients with recurrent/metastatic HNSCC. Two phase II studies including 30 recurrent/metastatic patients each have reported 50–70% responses. One of these studies has shown a median survival of 9 months [44,45]. Four randomized phase III studies have confirmed these results. The association of cisplatin (100 mg/m^2) and 5-FU (1000 mg/m^2/d for 4 days) administered every 3 weeks has given response rates between 27 and 32% and a median overall survival of 5.7–8.7 months [3,6,33,34]. But toxicity is important, with 67% of the patients experiencing neutropenia, 23% thrombopenia, 12–33% anaemia, 21% infections, 18–35% nausea and vomiting and 13–31% grade 3–4 mucositis. The study by

Table 2 Combination of chemotherapies for recurrent/metastatic head and neck squamous cell carcinoma (phase III trials, unless otherwise specified)

Chemotherapy regimen	Response (%)	Overall survival (months)	References
Cisplatin (100 mg/m^2/3 weeks) 5-FU (1000 mg/m^2/d, 5 days/3 weeks)	27–32	5.7–8.7	[3,6,33,34]
Cisplatin (75 mg/m^2/3 weeks) Docetaxel (75 mg/m^2/3 weeks)	33–54	9.6–11	[35–40] phase II
Cisplatin (75 mg/m^2/3 weeks) Paclitaxel (175 mg/m^2/3 weeks)	26–36		[33,41]
Carboplatin (AUC5/3 weeks) Paclitaxel (80 mg/m^2/week)	48–53	10.9–12.8	[42,43] phase II
Cisplatin (100 mg/m^2/3 weeks) 5-FU (1000 mg/m^2/d, 5 days/3 weeks) Cetuximab (400 mg/m^2 then 250 mg/m^2/week)	36	10.1	[34]

5-FU, 5-fluorouracil.

Forastiere *et al.* [3] has shown a higher response to combination chemotherapy than to weekly methotrexate alone (32 vs. 10%, respectively), but overall survival was not significantly different between the two arms. However, as noted above, in HNSCC patients, higher response rates are often correlated with better quality of life. This is why the association of cisplatin-5-FU has become a standard in the treatment of selected patients with performance status (PS) 0–1. In the same study, the researchers studied the clinical efficacy of the combination of carboplatin and 5-FU: the response rate was lower than with cisplatin-5-FU (21 vs. 32%) with an overall survival of 5 months (not significantly different). These data are consistent with the consensus that carboplatin is less effective than cisplatin, even if this point has not been formally shown in a randomized study.

Cisplatin and taxanes

The data concerning this association result essentially from phase II studies. The level of proof is thus low and results must be viewed with caution.

In the first-line treatment of recurrent/metastatic HNSCC, the combination of cisplatin (75 mg/m^2)–docetaxel (75 mg/m^2), administered every 3 weeks, has produced response rates between 33 and 53.7% and a median survival of 9.6–11 months [35–40]. Tolerability has been acceptable with only 10–15% of grade 3–4 toxicities, mostly neutropenia, despite granulocyte colony-stimulating factor support. The results of larger studies are awaited.

Several phase II studies have shown that the association of cisplatin–paclitaxel induced response rates between 32 and 48% and an overall survival of 10–11 months [46–48] with acceptable tolerance, even if haematological toxicity was important. Two phase III studies have failed to show any significant superiority of the combination over cisplatin–5-FU, with poorer drug tolerance [33,41]; this association is thus not recommended in patients with recurrent/metastatic HNSCC.

As both the combinations are toxic, several researchers have tested the association of carboplatin and paclitaxel. Phase II studies have shown response rates between 25.9 and 43% and a median overall survival between 7.2 and 15.7 months [49–52]. Toxicity remained important, in particular, haematological toxicity. As in breast cancers, tolerance and efficacy are improved by weekly administration of paclitaxel; this schedule was also tested in HNSCC patients. Two studies were conducted using the association of carboplatin (weekly or every 3 weeks) and paclitaxel (80 or 100 mg/m^2, weekly). The rates of response were 48 and 53% and the median survival was 10.9 and 12.8 months, respectively [42,43]. Tolerability was improved. This association can thus be proposed for the treatment of patients with altered PS (2 or >2).

Cisplatin and cetuximab

Although preclinical data were encouraging, results from the first phase II studies have been disappointing. Baselga *et al.* [53] have found only 13% responses with the cetuximab–cisplatin combination. A phase III study using this association showed an increase in the response rate from 10 to 26% [5], but the difference in overall survival was not statistically significant (8–9.2 months). There was probably a lack of power because the number of patients was low (123 recurrent patients). In this trial, no maintenance treatment with cetuximab was given after the six courses of cisplatin (100 mg/m^2 every 4 weeks), either alone or in association with cetuximab (weekly), and patients could cross over to cetuximab after progression: these two points may explain the absence of a statistically significant difference in overall survival. In another phase III study, 442 patients were randomized to one of the two arms: cisplatin (100 mg/m^2 every 3 weeks)-5-FU (1000 mg/m^2/d for 4 days every 3 weeks) and cetuximab or placebo [34]. After six courses of chemotherapy, weekly administration of cetuximab could be continued for maintenance until progression. The response rate was significantly increased from 20 to 36%, and progression-free survival (from 3.3 to 5.6 months) and overall survival (from 7.4 to 10.1 months) [hazard ratio = 0.80; 95% confidence interval = 0.64–0.99; $P = 0.04$). There were more febrile neutropenia (nine patients vs. one, $P = 0.02$), more cutaneous toxicities (but only 9%

grade 3–4) and more allergic reactions. After this study, the association of cisplatin–5-FU–cetuximab has become the standard first-line chemotherapy regimen for all patients with preserved general status PS (0–1).

Taxanes and epidermal growth factor receptor inhibitors

This association has been essentially tested after the failure of the platinum-based chemotherapy. In this context, two phase II studies have reported interesting response rates: 60% for the study evaluating the association of paclitaxel–cetuximab [54]; 12% with an overall survival of 7 months for the study evaluating the association of docetaxel–cetuximab [55]. A phase III trial testing the combination of gefitinib and docetaxel in platinum-resistant patients has shown a small, but not significant, increase in the response rate (6–14%) without benefit in overall survival (6 months for docetaxel alone versus 6.8 months for the combination) [11]. However, gefitinib is probably not the most effective EGFR inhibitor as it does not induce antibody-dependent cell cytolysis, contrary to cetuximab.

Conclusion

In recurrent/metastatic HNSCC, chemotherapy, principally polychemotherapy, improves the quality of life and survival of a patient. The median survival of patients with PS (0–1) is currently longer than 10 months when treated with the triplet, cisplatin–5-FU–cetuximab. For patients with PS (2–3), treatment is based either on the combination of carboplatin–paclitaxel or on monotherapy with methotrexate, cetuximab or weekly administration of paclitaxel. Despite these treatments, survival remains poor and new strategies are awaited. Targeted therapies could help increase treatment efficacy; these treatment options are discussed in detail in another article of this special issue.

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