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The chemotherapy of head and neck cancer

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Studies of combination therapy [with agents such as cisplatin, 5-fluorouracil (5-FU) and methotrexate] have shown some improvements in response rate; however, no obvious survival advantage over monotherapy in the treatment of patients with metastatic or advanced locoregional cancer of the head and neck have been observed. In the neoadjuvant setting, chemotherapy is helpful in preserving the larynx and hypopharynx but has no proven impact (positive or negative) on survival. New treatment options are needed to improve survival in head and neck cancer. Among the new options for chemotherapy in metastatic/recurrent disease is docetaxel. With monotherapy, response rates of 23–42% are seen, and, when used in combination with cisplatin and 5-FU, response rates of 52–100% have been reported in phase I/II trials. A phase III trial of the addition of docetaxel to standard neoadjuvant therapy with cisplatin and 5-FU is now underway. [© 1999 Lippincott Williams & Wilkins.]

Key words: 5-Fluorouracil, cisplatin, docetaxel, head and neck cancer.

Introduction

Head and neck cancers account for 5% of all adult malignancies and 2% of all cancer deaths.[1–3] Forty percent of patients present with early stage I and II disease, in this setting radiotherapy and surgery can be curative.[2,3] However, 60% of patients with head and neck cancers present with advanced locoregional disease. Of these patients, less than 30% are alive at 5 years after conventional surgery plus radiotherapy.[2,3] Between 60 and 70% experience a recurrence within 2 years, and 20–30% develop distant metastases. For these patients there is at present no treatment which offers the chance of cure.

Nevertheless, there are options for therapy in head and neck squamous cell carcinoma (HNSCC). Neoadjuvant therapy may improve survival and allow organ preservation; and chemotherapy can be given in the adjuvant setting, concomitant or alternating with radiotherapy.

Chemotherapy in metastatic recurrent disease

Several classical agents have proven activity in recurrent and metastatic HNSCC. Response rates of 21% have been reported with bleomycin, 26% with carboplatin, 15% with 5-fluorouracil (5-FU) and 15% with cyclophosphamide.[3–7] However, the most active agents are methotrexate (response rate 31%) and cisplatin (response rate 28%).[3–7]

An EORTC study[4] compared three regimens, i.e. a combination of cisplatin, methotrexate, bleomycin and vincristine (CABO), a combination of cisplatin plus 5-fluorouracil (5-FU) and cisplatin monotherapy, in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (Table 1).

Although the response rates were higher among patients treated with the four-drug combination, the overall durations of median survival (29 weeks for all patients) were not statistically different across the three arms of the study. A second important finding (which has clear relevance to the interpretation of studies and particularly phase II trials) was the importance of performance status and prior treatment as prognostic factors. Age, sex, site, and extent of disease and tumor differentiation were non-significant factors on multivariate analysis.

Three other studies have compared single-agent with combination therapy or combination studies

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Table 1. Combination therapy in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC): the EORTC study[4]

	CABO	Cisplatin + 5-FU	Cisplatin
No. of evaluable patients	127	116	12
Efficacy			
Complete response	10%	2%	3%
Partial response	27%	32%	13%
Progression-free survival	19 weeks	17 weeks	12 weeks
Toxic deaths	3	1	–

CABO, cisplatin, methotrexate, bleomycin and vincristine; 5-FU, 5-fluorouracil.

Table 2. Patient characteristics of the EORTC 24891 study comparing surgery alone to neoadjuvant chemotherapy[9]

	Surgery alone arm	Chemotherapy arm[a]	Total
No. of randomized patients	99	103	202
No. of eligible patients	94	100	194
Pyriformis sinus	74	78	152
Aryepiglot fold	20	22	42
Stage of disease			
II	6	7	13
III	51	59	110
IV	37	34	71

[a]Chemotherapy comprised of cisplatin + 5-fluorouracil.

with each other. Thus Jacobs *et al.*[5] compared cisplatin and 5-FU as single agents and in combination. In this study the combination of cisplatin and 5-FU produced an overall response rate (ORR) of 32% with a median survival of 5.5 months compared to an ORR of 17% (median survival 5.0 months) and 13% (median survival 6.1 months) for single-agent cisplatin and 5-FU, respectively.[5] The study by Forastiere *et al.*, which compared cisplatin plus 5-FU versus carboplatin plus 5-FU versus methotrexate, achieved similar results for the cisplatin and 5-FU combination (with a response rate of 32%, median survival 6.6 months versus carboplatin plus 5-FU: response rate of 21%, median survival 5 months versus methotrexate: response rate of 10% and median survival of 5.6 months).[6] The Liverpool study observed response rates of 14% (median survival 6 months) with cisplatin alone versus response rates of 12% (median survival of 5.5 months) with cisplatin plus 5-FU versus a response rate of 6% (median survival 2 months) with methotrexate alone versus an 11% response rate (median survival 6 months) with the cisplatin and methotrexate combination.[7] However, none of these trials showed any advantage for combination therapy over monotherapy in overall duration of survival, which remained stubbornly fixed at around 6 months.

The lack of evidence for the superior efficacy of combination regimens, combined with their greater toxicity, justifies the view that monotherapy is currently the treatment of choice for patients with metastatic or advanced locoregional HNSCC. The situation, clearly, is one in which there is a desperate need for active new agents.

Neoadjuvant chemotherapy

The use of chemotherapy in the neoadjuvant setting is aimed at enhancing survival or organ preservation. The EORTC has conducted a trial in 202 previously untreated patients with carcinoma of the hypopharynx.[9] Patients were randomized either to receive immediate surgery (n = 99) or chemotherapy with three courses of cisplatin (100 mg/m^2) plus 5-FU (1000 mg/m^2/day on days 1–5) (n = 103) (Table 2). The response rates among the 97 patients who actually received chemotherapy was 86% (comprising of 54% of patients with complete response and 32% of patients

Table 3. An overview of single-agent docetaxel administered at a dose of 100 mg/m² as a 1 h i.v. infusion every 3 weeks in the treatment of head and neck cancer[10–12]

	Posner[10]	Catimel[11]	Couteau[12]
No. of patients	31	42	24
Metastatic disease	10%	28%	92%
Locoregional recurrence	84%	65%	NA
Both recurrent and metastatic disease	6%	7%	NA
Response			
Complete response	14%	5%	0%
Partial response	29%	24%	23%
Overall response rate	42%	32%	23%
Median duration of response (range)	5.7 months (2–14+)	6.5 months (2.7–8.8+)	17 weeks

NA, not available.

with partial response). Importantly, this study found nothing to confirm the previous suspicion that chemotherapy might compromise survival by delaying surgery. Three-year data in fact showed a non-significant trend towards a higher rate of survival among chemotherapy-treated patients (57 versus 43%), longer median survival (44 versus 25 months) and a lower risk of developing distant metastases (25 versus 36%).

Induction chemotherapy does aid in organ preservation and the data now show it can be given without compromising survival. Further, it seems at least possible that effective chemotherapy administered relatively early in the disease may favorably influence outcome.

New single agents

The traditional approach to chemotherapy in HNSCC is likely to be influenced by the development of active new agents such as gemcitabine, topotecan, paclitaxel and docetaxel.

Three studies have been conducted with single-agent docetaxel 100 mg/m² in patients with recurrent and/or metastatic disease (Table 3).[10–12] Posner *et al.* reported a 42% response rate (14% complete response and 29% partial response) in 31 patients, with a median survival of 5.7 months.[10] Catimel *et al.*[11] reported a response rate of 32% in 42 patients and Couteau *et al.*[12] observed a response rate of 23% in 24 patients (Table 3). The median durations of survival in the last two studies were 6.5 months and 17 weeks.

Following this evidence of good single-agent activity, several trials have studied docetaxel in combination with other active agents in HNSCC, notably cisplatin and 5-FU (Table 4).[13–19]

Although the number of patients involved in these phase I/II studies was relatively small and their performance status good, the response rates reported are undoubtedly high. In the study by Schoffski *et al.*,[13] the ORR of 56% included an 80% response rate in patients with locally advanced disease.

The highest response rate, however, was seen in the trial of four agents in combination.[15,16] All patients responded and there was a 67% complete response rate, with a 33% partial response (i.e. ORR of 100%).[15,16] In this trial of previously untreated HNSCC, 23 patients received cisplatin 25 mg/m² per day plus leucovorin 500 mg/m² and 5-FU 700 mg/m² (all administered as continuous infusion on days 1–5) together with docetaxel 25, 45 or 60 mg/m² as a 1 h i.v. infusion on day 1. In view of the expected toxicity, prophylactic granulocyte macrophage colony stimulating factor (G-CSF) and ciprofloxacin were administered from day 5 onwards. The dose-limiting toxicities were febrile neutropenia, renal tubular concentrating defects and mucositis. As expected with this combination, diarrhea and fatigue were also observed. The maximum tolerated dose of docetaxel was 60 mg/m².

Discussion

The promising data following combination of docetaxel with cisplatin and/or 5-FU justify further trials. These should be undertaken both with the aim of palliation, in patients with recurrent disease

Table 4. An overview of phase II studies with docetaxel in combination chemotherapy in the treatment of head and neck cancer[13–19]

	Schoffski[13]	Janinis[14]	Posner[15,16]	Forestiere [17]	Kienzer[18]	Tubiana-Mathieu[19]
Treatment (mg/m^2)						
Docetaxel	100	80	26–60	75	80	80
Cisplatin	75	40	25	75	70	–
5-Fluorouracil	–	1000	700	–	–	1000
Leucovorin	–	–	500	–	–	–
No. of enrolled patients	43	21	20	33	29	36
No. of evaluable patients	42	21	17	33	21	26
Median age in years (range)	55 (35–76)	56 (40–72)	51 (32–66)	51 (21–72)	NA	NA
Male : female ratio	40 : 3	18 : 3	NS	28 : 5	NA	NA
Performance status	0–1[a]	0–1[a]	16 = 0[b]	25 = 1[b]	NA	NA
Response						
Complete response	9.3%	25%	67%	9%	5%	5%
Partial response	46.3%	50%	33%	42%	53%	20%
Overall response rate	55.6%	75%	100%	52%	76%	25%
Stable disease	7.0%	19%	–	18%	19%	45%

[a]World Health Organization performance status; [b]Performance status. NA, not available.

and intent to cure, in the neoadjuvant setting in therapy-naive patients. A pilot phase III study in which patients were randomized before surgery and/or radiotherapy to either cisplatin plus 5-FU or cisplatin plus 5-FU plus docetaxel has already been started.

This new agent has provided promising initial results both as a single agent and in combination in the treatment of recurrent or metastatic head and neck cancer. It is hoped that the incorporation of docetaxel in the neoadjuvant setting will result in an increase in survival. Results from ongoing phase II and III studies are awaited to confirm the initial results and hopefully provide new treatment options.

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