

Chemotherapy Options for Patients With Metastatic or Recurrent Squamous Cell Carcinoma of the Head and Neck

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ABSTRACT

The purpose of this review is to provide readers with guidance concerning treatment of patients with advanced, recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) in the context of clinical trial data. We discuss issues surrounding the treatment of patients with SCCHN, with an emphasis on recommendations based on results from phase II and III clinical trials published since 1980. Many options exist for the treatment of patients with SCCHN. The most important decisions involve determining which patients are in need of treatment and which are most likely to benefit from treatment. Although many chemotherapy treatments have been shown to induce responses, survival improvement remains an unfulfilled goal. Definitive data do not exist on the effects of chemotherapy on quality of life or progression-free survival as measures of clinical benefit in this setting. Performance status, history of prior treatment, extent of tumor, and need for palliation are the most important factors in the decision to treat a patient with chemotherapy for incurable SCCHN. Single-agent treatment with conventional doses of methotrexate remains a standard for most patients with advanced, recurrent or metastatic SCCHN. Cisplatin plus fluorouracil, cisplatin plus a taxane, and single-agent taxane are the most widely studied alternatives. There is a need for further trials with end points other than overall survival or tumor response in this patient population. Guidelines for patient selection and treatment options are provided.

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INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) region is one of the more chemotherapy-sensitive human neoplasms. Response rates approaching 70% have been reported with single-agent treatment, and recent reports demonstrate that overall response rates and complete response rates approaching 90% and 60%, respectively are achievable.¹⁻³

Despite the advances made in the treatment of patients with SCCHN confined to the primary and neck region, many of these patients still relapse and are not candidates for salvage surgery or radiation treatment. Most of these patients die as a result of complications of their cancer.^{4-6,7} Additionally, patients present with metastatic disease and are therefore not eligible for multimodality potentially curative treatment.

Because patients with recurrent or metastatic disease are generally incurable, the goals of treatment are more limited, and include prolongation of overall survival (OS) or progression-free survival (PFS), palliation of existing symptoms, and prevention of new cancer-related symptoms. While improvement in survival has been the holy grail of treatment in this setting, no chemotherapy treatment has been convincingly demonstrated to prolong survival. Additionally, a correlation between

tumor shrinkage and benefit such as symptom reduction or improvement in quality of life has not been rigorously evaluated. These factors underscore the importance of clinical trials for this patient group.

THE INITIAL EVALUATION: WHICH PATIENTS ARE MOST LIKELY TO BENEFIT FROM TREATMENT?

Multivariable analyses from palliative chemotherapy clinical trials have shown that time to progression and survival are greatly influenced by factors other than the specific chemotherapy administered. Poor performance status, prior treatment (chemotherapy, surgery, or radiation), and advanced stage of disease are all associated with a marked reduction in the response rate to chemotherapy. These three factors plus lack of response to chemotherapy are strongly correlated with shorter survival duration, suggesting that for single-arm clinical trials, patient selection has been at least as important as the type of therapy administered.⁸⁻¹¹ Therefore, response to chemotherapy may be a prognostic marker for patients destined to do well. The fundamental question concerning the survival benefit of any chemotherapy treatment remains unanswered because an adequately powered randomized, controlled clinical

trial comparing chemotherapy treatment with supportive care has not been performed.

Additional predictors of poor outcome or shortened survival that should be considered when making treatment decisions include the presence of hypercalcemia and comorbidities such as poor cognitive function; ongoing heavy tobacco, alcohol, or other carcinogen use; and the absence of a strong social support system.¹²⁻¹⁴ For example, even in the era of bisphosphonates, the prognosis for SCCHN patients with hypercalcemia is dismal, with median survival of 35 days.¹⁵

Table 1 summarizes the main adverse prognostic features in patients with SCCHN. One can anticipate that patients without these adverse outcome predictors would be more likely to benefit from palliative chemotherapy.

CHEMOTHERAPY TREATMENT OF SCCHN: A HISTORICAL PERSPECTIVE

Before US Food and Drug Administration approval of cisplatin (CDDP) in 1978, the role of the medical oncologist was strictly palliation of patients with advanced incurable disease. Methotrexate (MTX) and bleomycin were the most widely used cytotoxics.

Response rates to MTX as high as 77% have been reported in patients with no prior treatment.¹⁶ The most widely studied and used dosing is weekly intravenous administration of 40 to 60 mg/m². Higher doses of MTX are associated with both increased response rates and toxicity, but do not improve survival.^{17,18} Response rates to bleomycin are in the 15% to 20% range.

As early as 1977, CDDP was found to induce rapid responses in 30% of patients who had been heavily pretreated with surgery, radiation, and chemotherapy. Higher response rates were seen in patients without prior treatment.^{19,20}

Other cytotoxics shown to have response rates exceeding 15% included carboplatin (CARBO), cyclophosphamide, doxorubicin, hydroxyurea, vinblastine, and fluorouracil (FU). Table 2 summarizes the response data for agents with clinically relevant single-agent activity against SCCHN.

Table 1. Factors Associated With Worse Outcomes in Patients With SCCHN Treated With Systemic Chemotherapy for Advanced and/or Metastatic Disease

Factors
Patient related
Poor performance status
Presence of comorbidity
Poor cognitive functioning
Lack of social support
Ongoing carcinogen use
Tobacco
Betel quid
Alcohol
Disease related
Advanced stage, bulky locoregional, or metastatic disease
History of aggressive disease
Hypercalcemia of malignancy
Treatment related
Prior treatment
Lack of or minimal response to treatment

Through the early 1980s, MTX, CDDP, FU, and bleomycin were regarded as the most useful agents in SCCHN on the basis of objective response rates.⁸⁻¹⁰ Only one small study was designed to demonstrate clinical benefit over supportive care using randomized controlled trial (RCT) methodology. In this trial, 31 patients treated with single-agent CDDP demonstrated prolonged survival compared with 26 patients treated with supportive measures.²¹ This same trial demonstrated that patients who respond do so quickly. Of the 16 responders, 75% responded after the first cycle and the remaining 25% after the second cycle.

RANDOMIZED TRIALS OF NON-TAXANE REGIMENS AND META-ANALYSIS

In the 1980s, a number of RCTs compared various combinations of platinum and other chemotherapeutics (Table 3). The outcome of these trials analyzed individually can be summarized as follows: CDDP as a single agent is not superior to MTX in terms of response or median survival.²² The combination of CARBO and MTX is not superior to MTX alone.²³ Multiagent chemotherapy in general is associated with higher response rates than single-agent treatment. CDDP- and multiagent-containing regimens are associated with more high-grade toxicity than single-agent treatment. Platinum-containing combination regimens have the highest response rates, occasionally approaching 50% in the RCT setting.²⁴⁻²⁷ None of these trials have demonstrated a survival superiority of one regimen versus another.

Meta-analytic evaluation and interpretation of a subset of trials from this era demonstrated a statistically significant response superiority to combination versus single-agent treatment, but paradoxically the median survival trends slightly favored single agents over combinations.²⁸ Only the response and survival results for CDDP + FU versus single agents and other combinations were not discordant. Probably the most salient piece of survival information from this meta-analysis was that the difference in median survival in all comparisons was quite modest: 4 to 25 days. There was a substantial increase in nausea and vomiting associated with CDDP + FU regimens. However, these and many of the subsequently discussed controlled trials were conducted in the era before the widespread use of effective 5-HT3 receptor antagonists for nausea.^{29,30}

CDDP AND FU

The combination of CDDP + FU emerged as a favored treatment regimen in the 1980s and 1990s. This was based initially on two phase II trials published in the mid-1980s testing induction chemotherapy, in which response rates of 67% and 70% with complete response rates of 19% and 27% were seen.^{31,32} Response rates were notably lower for the subsets of patients who had prior surgery and radiation and those who had metastatic disease.

Results from two RCTs designed to compare platinum + FU with single-agent chemotherapy in patients with advanced SCCHN were published in 1992 (Table 3). The first trial compared CDDP + FU and CARBO + FU with MTX. The second trial compared CDDP + FU with CDDP and FU as single agents.^{33,34} The overall response rates to CDDP + FU and CARBO + FU were 32% and 21%, respectively.

Table 2. Phase II Trial Single-Agent Response Rates in Patients With Advanced SCCHN

Agent	No. of Patients Assessable	Response Rate (%)	Median Survival (months)	Year of Publication	Reference
Methotrexate		8-77 (average 31)		1984	9,8
Bleomycin		6-45 (average 21)		1977-84	9,89
Cisplatin		14-41 (average 28)		1983-94	9,34,35,90
Carboplatin		25		1986	91
Oxaliplatin		10		1996	71
Cyclophosphamide		36		1980	92
Doxorubicin		24		1980	92
Hydroxyurea	18	39		1980	10
Vinblastine		29		1980	10
Vinorelbine		6		1994	74
Fluorouracil		15		1984	9
Gemcitabine	61	13		1994	93
Capecitabine	14	8		2003	94
Orzel	42	21		2001	95
Irinotecan		0-14		2005	72
Paclitaxel 24-hour infusion	34	40 (4 CRs)	9.2	1998	39
Paclitaxel 96-hour infusion	Chemotherapy naïve/paclitaxel naïve/paclitaxel exposed	13/0/0	5.5	2004	41
Docetaxel		21-42		1994-2005	36-38,96
Pemetrexed	35	26	6.4	2001	97
Ifosfamide		26		2003	69
Cetuximab	103	13		2005	75
Erlotinib	115	4		2004	73
Gefitinib	47	11	8.1	2003	70
Sorafenib (BAY 43-9006)	10	6 SD (60%); 4 SCCHN + 2 NPC; range, 3-6 cycles		2005	87

Abbreviations: SCCHN, squamous cell carcinoma of the head and neck; CR, complete response; SD, stable disease; NPC, nasopharyngeal carcinoma.

The response rates to the single-agent treatments were 17% to CDDP, 13% to FU and 10% to MTX, all significantly lower than CDDP + FU. Median survival, however, was approximately 6 months for all treatment arms. Grade 3 to 4 toxicity rates with CDDP + FU were nearly double the rates of the other treatment arms.

In 1994, one of the largest studies (382 patients) published to date in this patient population compared CDDP + FU and CABO (CDDP + MTX + bleomycin + vincristine) with CDDP alone. Both the CDDP + FU and CABO arms demonstrated higher response rates and time to progression (TTP) than CDDP, but median survival was 7.3 months in all arms, and high-grade toxicity occurred more often in the combination arms, with CDDP + FU being the highest.³⁵

In summary, when using response rates as the clinical trial end point for recurrent disease, CDDP-based combinations appeared to be superior to single agents, but at a cost of greater toxicity and without demonstrating improved survival or other indicators of clinical benefit.

THE TAXANES

During the 1990s, a large number of new agents were tested in patients with advanced SCCHN (Table 2). Both docetaxel and paclitaxel stood out as having high single-agent response rates (21% to 42%),³⁶⁻⁴⁰ but were accompanied by high rates of severe toxicity. Because many of

these trials were limited to patients with excellent performance status, it is possible that the high response rates were at least partially caused by patient selection. Paclitaxel 250 mg/m² on the 24-hour infusion schedule every 3 weeks was associated with hospitalizations for febrile neutropenia in 15% of patients in one trial and four early deaths from sepsis in another.^{39,40} Docetaxel administered at 100 mg/m² as a 1-hour infusion resulted in a 53% rate of febrile neutropenia.³⁷ Attempts to increase the therapeutic index of paclitaxel in patients with advanced SCCHN by changing the schedule of infusion have been variably successful.⁴¹ Subsequent routine use of taxanes in SCCHN patients has been at lower doses with shorter infusion schedules (docetaxel, 1 hour; paclitaxel, 3 hours) to increase tolerability. There is a clinical impression that bone marrow suppression is reduced, whereas significant anticancer activity persists; however, there are no RCTs to confirm this impression.

Although some investigators have emphasized the potential therapeutic differences between docetaxel and paclitaxel, there have been no direct comparisons in SCCHN patients to confirm this hypothesis.^{42,43} However, a large experience from other tumor types is instructive.⁴⁴⁻⁴⁷ In cancers responsive to taxanes, docetaxel and paclitaxel are reasonably active on both the weekly and every-21-days schedules. Docetaxel administered every 3 weeks is probably more active and associated with more adverse events than when administered on a weekly schedule, whereas weekly paclitaxel may be both

Table 3. Randomized Clinical Trials of Chemotherapy in Advanced/Metastatic SCCHN

Trial	No. of Patients	Response Rate % (CR %)	Median Survival (months)	Reference	Year of Publication	High-Grade Toxicity*
CDDP ± cetuximab	117†	26 v 10	9.2 v 8.0	84	2005	173 v 93
CDDP + FU v CDDP + Tax	218†	27 v 26	8.7 v 8.1; OS at 1 year, 41% v 32%	64	2005	334 v 198
MTX v docetaxel (weekly)	57	15 (5) v 27 (3)	3.7 v 3.9	54	2004	6 v 21
CDDP + high-dose Tax v CDDP + conventional Tax	210†	35 v 36	7.6 v 6.8	65	2001	321 v 320
Raltitrexed + CDDP + FU/LV v MTX + CDDP + FU/LV	72	81 (28) v 42 (8)		100	2002	67 v 32
Edatrexate v MTX	264†	21 v 16	6 for both groups	101	1995	90 v 45
CABO v CDDP + FU v CDDP	382†	34(9.5) v 31 (1.7) v 15(2.5)	7.3 (TTP, 4.8 v 4.3 v 3)	35	1994	34 v 35 v 20
MTX ± lonidamine	89	26 (10.5) v 18 (0)		102	1994	78 v 41
CDDP 100 mg/m ² + FU 4 g/m ² q21d v CBDCA 300 mg/m ² + FU 4 g/m ² q21d v MTX 40 mg/m ² wkly	277†	32 v 21 v 10	6.6 v 5.0 v 5.6	33	1992	66 v 47 v 35
CDDP 100 mg/m ² + FU 4 g/m ² v CDDP 100 mg/m ² v FU 4 g/m ² ; all q21d	249†	32 v 17 v 13	5.7 for all groups	34	1992	77 v 34 v 32
CBDCA + MTX v MTX	40†	25 v 25	3 v 2	23	1989	
CABO v CDDP	209†	30 v 15	9 (TTP, 4.5)	24	1988	57 v 11
CABO v vincristine + MTX + Bleomycin	185†	50 (16) v 28 (5)	9 (TTP, 4.5 v 3.5)	25	1987	35 v 41
CDDP + bleomycin + vincristine v MTX	191	24 v 16	7.2 v 7.8	27	1986	43 v 57
Control v bleomycin v CDDP + bleomycin v CDDP	117	n.a. v 14 v 24(5) v 13 (3)	NS except CDDP arms v others 4.3 v 1.8	21	1985	NA v 4 v 25 v 24
MTX + bleomycin + CDDP v MTX	163†	48(16) v 35(8)	5.6 for both groups (TTP, 3.5)	26	1985	
CDDP v MTX	100†	8 v 16	4.5 v 5	22	1985	260 v 174
High-dose (1.5 g/m ²) MTX + LV v conventional (40 mg/m ²) MTX	47†	32 v 22	4.2 for both groups	17	1984	30 v 10

NOTE. Boldfacing indicates $P \leq .05$.

Abbreviations: CDDP, cisplatin; FU, fluorouracil; OS, overall survival; MTX, methotrexate; LV, leucovorin; q21d, every 21 days; CBDCA, carboplatin; CABO, CDDP + MTX + bleomycin + vincristine; TTP, time to progression; Tax, paclitaxel; CR, complete response; NS, not significant; NA, not assessable.

*Wherever toxicity was quantified by grade, relative number or percentage of grade 3 to 5 toxicities are reported. This is a sum of the worst event per patient for each toxicity type based on either absolute values or percentages reported in the publication.

†Majority of patients on this trial had prior therapy (excluding chemotherapy).

better tolerated and more efficacious than when administered every 21 days.^{48-50,51} Docetaxel seems to be more bone marrow and GI toxic than paclitaxel, whereas paclitaxel is more neuropathic than docetaxel, but neither of these adverse event profiles have not been associated with a worse quality of life.^{49,52,53}

There are limited data concerning single-agent taxane treatment versus other single agents. One RCT of MTX versus docetaxel demonstrated higher response rates to docetaxel but no median survival difference.⁵⁴ Two trials comparing MTX with paclitaxel closed prematurely without publication of data because of lack of adequate enrollment and lack of sufficient activity in all arms, respectively.^{55,56}

Because of the high single-agent activity of the taxanes and the potentially nonoverlapping toxicity of taxanes and platinum, combinations of paclitaxel + CDDP, paclitaxel + CARBO and docetaxel + CDDP, have been tested extensively in patients with good performance status (0 to 1; Table 4).^{47,57-61} Response rates of 27% to 53% and median survival of 5 to 12 months were reported. These response rates and survival durations were promising compared with the historical CDDP + FU experience because many of these trials included patients with prior surgery and radiation treatment. Combinations of

taxanes plus FU have been less promising, with response rates of 25% or less.^{62,63} Trials of taxanes plus gemcitabine are ongoing.

Two RCTs have defined the utility of paclitaxel + CDDP in patients with recurrent or metastatic SCCHN. In one trial, 218 patients, mostly with recurrent disease, were randomly assigned between CDDP + FU and CDDP + paclitaxel. Response rates and median survival durations in the two arms were virtually identical, 27% and 8 months respectively. The 1-year survival rate was 41% for the CDDP + FU control arm and 32% for the CDDP + paclitaxel arm, but these differences were not statistically significant. The number of high-grade toxicities reported in the CDDP + FU arm exceeded those in the CDDP + paclitaxel arm by a factor of 1.6.⁶⁴ The second RCT of the CDDP + paclitaxel combination compared two doses of paclitaxel administered as a 24-hour infusion, 200 mg/m² and 135 mg/m².⁶⁵ Response rates and median survival in the two arms were statistically indistinguishable, approximately 35% and 7 months, respectively. Hematologic toxicity was thought to be excessive in both arms.

Aggressive triple-agent protocols such as paclitaxel, ifosfamide, and CDDP or CARBO (TIP and TIC), and docetaxel, CDDP, and FU (TPF) have response rates approaching 60% and complete response

Table 4. Selected Phase II Trials of Multiagent Chemotherapy in Advanced Metastatic or Recurrent SCCHN

Agent	No. of Patients Assessable	Response Rate (%)	Survival (months)	Year of Publication	Reference
Cisplatin + fluorouracil					
Locally recurrent post-XRT	19	89	8	1984	32
Metastatic	11	36	6		
Overall	30	70 (27% CR)			
Cisplatin + fluorouracil					
No prior treatment	31	84 (23% CR)		1985	31
Recurrent post-XRT	30	50 (1% CR)	9		
Docetaxel + fluorouracil	17	24		2000	63
Prior chemotherapy	20	25		2004	62
No prior chemotherapy	43	19			
Paclitaxel + cisplatin					
3-hour IV	36	41 (6 CR)	11	2004	47
No prior chemotherapy; 3-hour IV	50	32 (10% CR)	10	2002	61
Paclitaxel + carboplatin					
Paclitaxel 3-hour IV	37	27 (3% CR)	4.9	2001	59
Paclitaxel 1-hour IV weekly	31	52 (3 CR)	12.8	2003	57
Docetaxel + cisplatin	40	53 (18% CR)	11	2002	58
No prior chemotherapy	34	53 (17% CR)		2002	60
Cisplatin + vinorelbine	42	33 (10% CR)	6	2002	98
TIP					
Paclitaxel 3-hour IV	53	58 (17% CR)	8.8	1998	66
TIC					
Paclitaxel 3-hour IV	56	59 (17% CR)	9.1	2001	67
TPF					
Chemotherapy naïve	19	44 (12.5% CR)	11	2000	68
Docetaxel + irinotecan					
Chemotherapy naïve	17	18	9.8	2005	99
Prior chemotherapy	34	3	4.9		
Cetuximab + cisplatin					
Prior PD to cisplatin	96	10	6.5	2005	81
Gefitinib, docetaxel, and cisplatin	24	50 (30% CR)		2005	82
Cetuximab + cisplatin or carboplatin					
No response to prior platinum	132	13	6.5	2005	83
Erlotinib + bevacizumab	48	15	6.8	2005	80
Gefitinib + celecoxib					
Prior chemotherapy	19	22		2005	79

Abbreviations: XRT, radiotherapy; CR, complete response; IV, intravenous infusion; TIP, paclitaxel + ifosfamide + cisplatin; TIC, paclitaxel + ifosfamide + carboplatin; TPF, docetaxel + cisplatin + fluorouracil; PD, progressive disease.

(CR) rates in the 15% range in patients with prior chemotherapy, median response durations of 4 to 7 months, and median survival of 9 to 11 months. Although these results suggest potential improvement over two-drug regimens, the best reported 1-year survival rate was 40% which was similar to recent trials of CDDP/FU but with added toxicity.^{1,3,66-68} Comparative trials are needed before recommending these regimens for use outside of a clinical trial setting.

RECENTLY TESTED AGENTS

Despite the large number of agents screened recently for anticancer activity against SCCHN in early clinical trials, the number of trials with positive results has been small (Table 2). Most of the active agents identified fall into a class of agents already known to have activity against SCCHN. Examples of new agents (and their respective single-agent response rates) in the same class as historically active agents in

SCCHN include ifosfamide (26%), pemetrexed (26%), oxaliplatin (10%), capecitabine (8%) and vinorelbine (6%). Active agents with relatively novel mechanisms of action or targets include irinotecan (14%), cetuximab (13%), gefitinib (11%), and erlotinib (4%).⁶⁹⁻⁷⁶

In general, the EGFR interactive agents have low single-agent activity in SCCHN, which is surprising given the high rate of EGFR overexpression in SCCHN and prominent activity in preclinical models.^{77,78} Preliminary data from combination trials of EGFR interactive agents with conventional chemotherapy are not encouraging.⁷⁹⁻⁸³ In phase II studies of refractory patients, response rates and survival are similar to what one would expect from the conventional chemotherapy or EGFR-targeted agents alone. An RCT of CDDP with or without cetuximab demonstrated no significant difference in PFS or OS, but a significantly higher response rate (26% *v* 10%). Additional toxicity with this combination consisted mainly of rash (Table 3).⁸⁴

Agents presently in clinical trials for which there are little to no data available include investigational agents targeting the microtubule

or mitotic apparatus, such as the epothilones and kinesin spindle protein inhibitors,^{85,86} and multiply targeted tyrosine kinase inhibitors such as lapatinib and sorafenib.⁸⁷ There are a plethora of agents targeting the vascular endothelial growth factor receptor and its ligand, both small molecules and monoclonal antibodies, presently in clinical trials. A major challenge to the development of these agents is the assumption that they will generate very little single-agent anticancer activity in the clinic, but may be useful in combination with conventional or other targeted therapies, as was the case for bevacizumab in colorectal, lung and breast cancers.⁸⁸

DISCUSSION AND TREATMENT GUIDELINES

During the last three decades, dozens of new agents have been tested on thousands of patients with metastatic or recurrent SCCHN. MTX, CDDP, CARBO, paclitaxel, docetaxel, and FU have demonstrated significant anti-SCCHN effect in many studies and alone or in combination are the mainstay of anticancer treatment for these patients today.

Unfortunately, it is unclear to what extent the use of these agents has brought about meaningful improvement in clinically relevant outcomes in this setting. No one agent or regimen is known to significantly increase survival compared to other agents. CDDP has been associated with increased survival versus supportive care in only one small study.²¹

The clinical benefit of tumor reduction in this setting has never been rigorously studied. However, for every case in which combination treatment containing CDDP has been associated with an improvement in response rate, the proportion of high-grade toxicity is greater as well (Table 3).

What can be recommended to the physician faced with such patients? Because there are no data on whether early or deferred treatment is preferred, timing of treatment should include consideration of present or risk of future symptoms based on the extent of tumor involvement of a vital organ or structure. The documentation of recurrent disease or presence of metastases should not in itself prompt a decision to begin treatment. Individualized decisions by the physician and patient in these circumstances should focus on benefits of palliation versus the risks of treatment toxicity. Once treatment is initiated, patients should be evaluated relatively early, within two cycles, for response and benefit. In the absence of early evidence of palliation of symptoms or tumor reduction, change or discontinuation of treatment should be considered. One caveat to this recommendation is that cytostatic agents now in clinical trials might require a different time course for evaluation of benefit.

Duration of treatment decisions for patients who experience response or palliation are difficult because some toxicities are cumulative and irreversible (eg, neuropathy). Generally patients should be treated until response stabilizes in CR or partial response plus an additional two cycles, but patients for whom palliation is evident and who have minimal adverse effects may be considered for extended treatment. Patients whose tumors do not respond to the first treatment choice are less likely to respond to alternate regimens, but patients with good performance status and significant need of palliation should not a priori be denied additional antineoplastic treatment.

We can make some observations concerning how to administer agents in this population. In the case of MTX, more is not better, and

40 to 60 mg/m² intravenously weekly continues to be an appropriate initial treatment for most patients.¹⁷ For paclitaxel, a 1-hour weekly infusion is preferred to a 3-hour or longer infusion on an every-21-days schedule. In the case of docetaxel, the largest experience is with the every-21-days regimen. CDDP may be preferred to CARBO in the curative treatment setting, but it is unclear whether there is an advantage in the palliation of recurrent disease. CARBO is associated with less nausea, vomiting, and kidney dysfunction.³³

Although both the taxanes and platinum agents are associated with high single-agent response rates, they are certainly more difficult to administer and more costly. Taxanes may be the treatment of choice for patients whose renal dysfunction precludes the use of MTX or CDDP. There are no data that persuasively make the case for the superiority of docetaxel or paclitaxel.

If response is paramount in the decision to treat a patient, then the combination of CDDP + FU or CDDP plus a taxane, despite the increased toxicity versus other treatments, may be the best choice. Some data suggest that the substitution of CARBO for CDDP diminishes response rates.³³ Therefore physicians and patients should be aware that better tolerability may compromise activity in this case. Table 5 lists some regimens in wide clinical use.

Physicians and patients should consider enrollment of patients onto clinical trials. Investigators should challenge themselves to consider settings in which supportive care arms would be acceptable controls, because poor enrollment has crippled trials with supportive care arms in the recent past (A. de Graeff, personal communication, February 2006). PFS and OS have been virtually unaltered in phase III trials of agents selected on the basis of response rates seen in screening phase II trials. Therefore, investigators should consider the possibility of different screening designs using more clinically relevant end points such as PFS, symptom control, or quality-of-life assessment earlier in a drug's development. Such designs would require greater numbers of patients per trial than is the standard today. Oncologists and patients should be reminded that without a significant increase in the number of patients willing to participate in clinical trials, progress will continue to be slow, for it is difficult to demonstrate incremental gains on the order of 10% to 15% with trials sized as they are today.

Table 5. Commonly Used Regimens for Treatment of Patients With Recurrent or Metastatic SCCHN:

Agent(s)	Dose and Schedule
Methotrexate	40-60 mg/m ² IV weekly
Paclitaxel	80-100 mg/m ² IV over 1 hour weekly
Docetaxel	75-100 mg/m ² IV over 1 hour every 21 days
Cisplatin + fluorouracil	Cisplatin 100 mg/m ² IV day 1 and fluorouracil 1,000 mg/m ² /d IVCI over days 1-4, every 21-28 days
Cisplatin + paclitaxel	Cisplatin 75 mg/m ² IV and paclitaxel 175 mg/m ² IV over 3 hours, both on day 1 and every 21 days
Cisplatin + docetaxel	Cisplatin 75 mg/m ² IV and docetaxel 75 mg/m ² IV over 1 hour, both on day 1 and every 21 days
Carboplatin + paclitaxel	Carboplatin AUC 6 and paclitaxel 200 mg/m ² IV over 3 hours, both on day 1, every 21 days or carboplatin AUC 2 and paclitaxel 80 mg/m ² IV over 1 hour, both on day 1 and weekly

Abbreviations: IV, intravenous infusion; IVCI, intravenous continuous infusion; AUC, area under the concentration-time curve.

Ultimately we must develop a better understanding of the basic mechanisms of the carcinogenic process, for this knowledge is essen-

tial to the development of new, more effective treatments that have substantial impact on survival rates and quality of life.

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