Systemic Therapy for Metastatic or Recurrent Squamous Cell Carcinoma of the Head and Neck

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Abstract

This article summarizes the systemic treatment options for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck, with an emphasis on recommendations based on phase II and III comparison trials of commercially available agents. Many single-agent and combination regimens have activity against these cancers, but improvement in overall survival remains a challenge, and median survivals in this population with best available therapy remain less than 1 year. The major recent advancement has been the introduction of epidermal growth factor receptor inhibitors, with mixed success. Although single-agent treatment with methotrexate, paclitaxel, docetaxel, or 5-fluorouracil remains one standard for many patients, the use of cisplatin- or carboplatin-based multidrug regimens that include cetuximab has become more popular, primarily based on one randomized study demonstrating a modest survival improvement of approximately 3 months associated with the addition of cetuximab. The burdensome adverse event profile of multidrug regimens makes appropriate patient selection for such aggressive treatment challenging, and consideration should include factors such as need for palliation, performance status of the patients, history of prior treatment, convenience, and cost. Genetically targeted and immunologically mediated treatments are promising but remain experimental. Given the worrisome prognosis for these patients, innovative clinical trials are a good option for many patients and deserve support. (*J Natl Compr Canc Netw* 2015;13:e37–e48)

The global burden of squamous cell carcinoma of the head and neck (SCCHN) is substantial. In 2014, an estimated 55,000 new cases were diagnosed in the United States and 500,000 globally, accounting for approximately 5% of the domestic and 8% of the global burden of new cancers.^{1,2} A substantial portion of these cancers are preventable through tobacco consumption interdiction and reduction in exposure to indoor smoke from sources such as wood burning stoves.³ In the United States, for example, a decline has already occurred in the incidence of most upper aerodigestive cancers, including SCCHN.¹ One notable exception to this is the exponential increase in the incidence of oropharyngeal SCCHNs, related to an increase in human papillomavirus (HPV)–associated oropharyngeal SCCHNs.⁴ HPV-related SCCHNs may also be preventable through vaccination strategies analogous to those for the prevention of uterine cervix cancers.

Despite this long-range optimism regarding prevention of many SCCHNs through vaccination against HPV and reduction of tobacco consumption domestically and globally, the burden of incurable disease remains high and is likely to remain so for the next few decades. Approximately half of all patients with SCCHN eventually die of their cancer, either because they have incurable metastatic disease at diagnosis or they experience disease relapse after attempts at curative treatment.⁵

Several randomized controlled trials have been performed in patients with recurrent or metastatic SCCHN over the past 30 years, with the most common design comparing a single agent with combination therapy. However, these randomized comparisons of different drug options are far from exhaustive, and data from uncontrolled clinical trials and expert clinician experience are regularly considered in clinical decision-making. It can be difficult to compare the clinical benefit of dif-

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ferent options because patient characteristics and history of prior therapy can vary widely among studies, and therapies used when a patient comes off a study are typically not reported, which confounds the interpretation of an overall survival (OS) end point. In addition, legacy studies were performed in an era during which the methodological standards for studies were both different and at times less rigorous compared with those of more modern studies. For example, many older studies have not used what are accepted now as rigorous criteria for response assessment, such as the RECIST system.⁶ Many studies only report response rates (RR) or progression-free survival (PFS), not both. Patients who experience disease relapse soon after chemoradiation are unlikely to derive substantial benefit from treatment using agents incorporated into the original chemoradiation regimen. Clinical trial reports are often vague about prior treatments, prior treatment responses, and time from prior treatment to the development of recurrent and/or metastatic SCCHN. Therefore, there can be considerable uncertainty concerning the anticancer activity that can be expected for an individual patient based on these reports.

Today most experts agree that the most clinically meaningful and robust outcome measurements are OS and PFS rather than tumor response rates. In the absence of analyses supporting a strong association between response rates and quality of life, one must be cautious about the assumption that higher RRs are associated with clinical benefit, especially because the higher RRs for cytotoxic agents are obtained at the price of a more burdensome adverse event profile, and improvement in OS compared with better-tolerated single agents has proved elusive. Therefore, whether patients with recurrent or metastatic disease are best served by concurrent multidrug treatment or sequential administration of individual chemotherapy agents is unclear.

Randomized trials that demonstrate improvement in survival compared with best supportive care or other drug therapy are rare,^{7,8} and the demonstrated survival advantage is a modest 2 to 3 months. Therefore, hope for OS improvement in the presence of recurrent or metastatic disease alone is not sufficient to justify routine immediate treatment with systemic agents in all patients, because most patients will experience a decrease in well-being unless those agents can relieve existing tumor-related symptoms.

Comparisons among treatments whose outcome differences in terms of OS and quality of life are modest, even though the costs of the compared therapy vary substantially, are fertile ground for cost-effectiveness and related value assessments. These circumstances are applicable to patients receiving treatment for recurrent or metastatic SCCHN. Finally, despite average or median outcomes, it is clear that a significant minority of patients experience unquestionable benefit from systemic treatments for their recurrent or metastatic disease. Until better predictors for who will benefit become available, clinicians and patients must often make decisions with significant uncertainty regarding benefit of these choices, but clinicians should be vigilant with respect to avoiding a default position of therapeutic nihilism for all of these incurable patients.

Single-Agent Uncontrolled Studies

Several agents have demonstrated robust anticancer activity in patients with recurrent and/or metastatic SCCHN. In the past few years several reviews and overviews have been published concerning systemic treatments for patients with recurrent or metastatic SCCHN.^{9–15} The most robustly studied agents are cisplatin, carboplatin, methotrexate, 5-fluorouracil (5-FU), ifosfamide, paclitaxel, and docetaxel (Table 1). Response rates typically range from 10% to 30%, with some outlier reports of higher response rates, typically in older, smaller studies in which patients had received no prior treatment. The choice between cisplatin and carboplatin is largely driven by one study that favored cisplatin over carboplatin when used in combination with 5-FU, based on superior response rates (32% vs 21%, respectively) without significant survival differences.¹⁶ Carboplatin is widely regarded as the more tolerable of these 2 platinums. Other agents occasionally used and less well studied include bleomycin, vinorelbine, cyclophosphamide, hydroxyurea, and gemcitabine, which are typically associated with response rates of 10% to 20%.^{17–20}

Epidermal growth factor receptor (EGFR) inhibitors, both anti-EGFR monoclonal antibodies and small molecule tyrosine kinase inhibitors, have recently been studied in patients with recurrent and/or metastatic SCCHN. When used alone, these agents generally have low levels of activity, with response

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Table 1 Selected Single-Agent Trials

Agent	N	Prior Treatments for Most	RR (%)	Median OS (mo)	Median PFS or TTP (mo)	Comments	Reference
Cisplatin	26	S, R, C	30	NA	NA	240 mg/m ² day 1 and 5, surgery day 12–15	58
Methotrexate	30	None; neoadjuvant trial	77 ^a	NA	NA	Intravenous and oral, various doses	59
Methotrexate	44	Mixed	66	NA	NA	dose levels 5000, 500, 50 mg/m ²	60
Methotrexate	58	Mixed	50, 21, 31	NA	NA	1250 mg/m ² days 1, 8 q21d	61
Gemcitabine	10	S, R, C	37	NA	NA	250 mg/m ² q21d	62
Paclitaxel	30	S, R, C (13% prior C)	40	9.2	TTP, 3.4	100 mg/m ² weekly	63
Paclitaxel	74	S, R, C (76% prior platinum)	29	14.3	TTP, 3.4	100 mg/m ² weekly	64
Docetaxel	30	S, R, C (63% prior platinum)	7	3.9	PFS, 1.8	35 mg/m ² weekly, 3/4 weeks	65
Docetaxel	23	S, R, C (100% prior platinum)	13	6.9	TTP, 2.1	30 mg/m ² weekly, 4/5 weeks	66
Docetaxel	38	S, R, C (45% prior platinum)	42	11.3	Response duration: median, 8.4	30 mg/m ² weekly	67
Docetaxel	31	S, R, C (32% neoadjuvant platinum)	42	NA	NA	100 mg/m ² q21d	68
Docetaxel	43	S, R, C (2% neoadjuvant cisplatin)	30	NA	NA	100 mg/m ² q21d	69
Zalutumumab	90	Platinum-refractory	5.7	5.3	PFS, 2.1		21
Cetuximab	103	Platinum-refractory	13	5.9	TTP, 2.3		22
Erlotinib	35	Neoadjuvant	29 ^a	NA	NA	Rash predicted response; EGFR expression did not	70
Erlotinib	115		4.3	6	PFS, 2.2	PS and rash predict response and OS	23
Gefitinib	52	S, R, C	10.6	8.1	TTP, 3.4	Dose escalation titrated to rash	24
Gefitinib	44	S, R, C	7	5.1	PFS, 1.9		25
Vinorelbine	24	S, R, C (24% prior PF)	22		Response duration, 5.8		71
Vinorelbine	16	S, R, C (94% prior platinum)	6	4.3	TTP, 1.9		72
S1	26	NA	46.2	NA	NA		73
UFT	42	S, R, C	21	8.7	NA		74
Capecitabine	40	S, R, C (65% prior platinum)	24	7.3	TTP, 4.8		75
Bleomycin	298		21				17
5-FU	118		15				17
Hydroxyurea	17		29				17
Ifosfamide	36	S, R, no prior C	28	6.8			76

Abbreviations: 5-FU, 5-fluorouracil; C, chemotherapy; EGFR, epidermal growth factor receptor; NA, not available; OS, overall survival; PF, cisplatin plus 5-FU; PFS, progression-free survival; PS, performance status; R, radiation; RR, response rate; S, surgery; TTP, time to progression; UFT, uracil and ftorafur.

^aNeoadjuvant means no prior treatment.

rates of 5% to 10% and correspondingly short PFS and OS intervals.^{21–25} Trials designed to escalate dose to acneiform rash as a surrogate pharmacodynamics marker have demonstrated no improvement in clinical activity beyond what was previously reported in trials using fixed-dose regimens, suggesting that dose optimization according to titration to rash is not beneficial.^{25,26}

Single-Agent Randomized Trials

Table 2 summarizes the data from selected randomized trials for patients with recurrent and/or metastatic SCCHN. Outcomes reported from these clinical trial are summarized herein.

Only 2 studies have compared any of these agents to a best supportive care (BSC) arm. In 1985, Morton et al⁷ published a 2 x 2 factorial design study of BSC versus bleomycin versus cisplatin versus bleomycin plus cisplatin. In this 116-patient study, no statistically significant differences in RR or OS were observed, except in the pooled analysis of cisplatin-containing arms versus the others, in which the median OS was 4.3 months with cisplatin versus 1.8 months without. This early study established cisplatin as the standard (alone or in combination) drug against which many subsequent agents have been tested. Machiels et al²⁶ compared zalutumumab, an experimental anti-EGFR monoclonal antibody, with BSC in 286 patients who had prior platinum exposure. The RR to zalutumumab was low at 6.3%, and the median OS (6.7 months) was not statistically different from that of BSC. This response rate approximates that of other anti-EGFR tyrosine kinase inhibitors and monoclonal antibodies (Table 1), suggesting a minor role, if any, for EGFR-targeted therapy alone.

Direct comparison of methotrexate versus cisplatin has yielded no clear winner, with modestly powered studies demonstrating numerical superiority of either cisplatin or methotrexate in terms of RR and median survival, depending on the study. No consistent pattern of superiority has been seen for either agent.^{16,27–29} A large trial comparing methotrexate with 2 dosage regimens of gefitinib in patients either unsuitable for or who experienced disease relapse after treatment with cisplatin similarly failed to demonstrate superiority for either therapy, with all arms' RR less than 10% and median survival ap-

proximately 6 months.³⁰ Additionally, a large study comparing cisplatin with 5-FU demonstrated no response or survival superiority for either agent.³¹ One small trial of methotrexate versus docetaxel in the first-line recurrent setting demonstrated no differences in RR, PFS, or OS.³²

Therefore, when deciding among these agents for single-agent treatment, data concerning antitumor efficacy does not offer much guidance. The most consistent and robust data are for cisplatin, methotrexate, and 5-FU, but the taxanes also probably should be considered. Although cetuximab is FDA-approved as a single agent in this setting, a 13% response rate, no evidence of superiority, and a dramatically higher price suggest that this agent should not be chosen over the others.

Multiagent Randomized Trials

A few dozen trials of multiagent chemotherapy have been performed in patients with recurrent and/or metastatic SCCHN. Tables 2 and 3 provide a summary of controlled and uncontrolled trials. Most of the randomized trials are small studies that have compared a methotrexate- or cisplatin-containing arm with something else. A major weakness with many of these studies is that they were inadequately powered to detect survival improvements. For example, to detect a 3-month (6 vs 9 months) difference in survival between 2 arms accruing over 2 years with a power of 0.9, more than 130 patients would need to be enrolled on each arm. Most randomized controlled trials of systemic chemotherapy fail to meet this adequate sample size criterion. Notably, of the 7 trials in Table 2 that have at least 130 patients per arm, only 1 yielded a statistically significant OS result. Subsequent therapy when a patient comes off study is typically not documented, which may also contribute to the lack of significant impact on OS.

Generally, response rates to combinations are higher than to single agents, but these higher response rates are associated with worse adverse event profiles and, with one exception, have not translated into survival improvement. The doublets of cisplatin plus methotrexate (PM), cisplatin plus 5-FU (PF), and cisplatin plus paclitaxel (PT) are all roughly equivalent in terms of response rates and survival.^{29,33,34} The comparison of PF and PM demonstrated approximately numerically similar adverse

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Table 2 Selected Randomized Trials

Agents	N	Prior Treatments for Most	RR (%)	Median TTP or PFS (mo)	Median OS (mo)	Comments	Reference
MTX vs CDDP	44	S, R	24 vs 29	2.8 vs 3.0	6.1 vs 6.3	87% emesis with CDDP	27
MTX vs CDDP + vincristine + B	61	S, R	33 vs 41		5.5 vs 4.0	Cost per course plus \$197 vs \$852	38
MTX vs CDDP	100	S, R, no prior C	16 vs 8	Response duration 4.5 vs 2.0	4.6 vs 4.0		28
MTX vs MTX + B + CDDP	163	S, R	35 vs 48	5.0 vs 5.8	5.6 vs 5.6		77
MTX vs CDDP + vinblastine + B	191		16 vs 24	4.6 vs 3.4	7.1 vs 6.7		78
CDDP vs CDDP + MTX	80	S, R	18 vs 33		6.3 vs 6.9	More AEs in combination, especially leucopenia and mucositis	79
MTX vs CDDP vs CDDP + MTX vs CDDP + 5-FU	124		19 vs 40 vs 31 vs 33		2.7 vs 8.7 vs 5.3 vs 6.7	OS significantly different only MTX vs CDDP	33
Control vs B vs CDDP vs CDDP + B	116	S, R	NA vs 14 vs 24 vs 13		No significant difference except CDDP vs control, 4.3 vs 1.8	2 x 2 trial design	7
CDDP + 5-FU vs CBCDA + 5-FU vs MTX	277	S, R	32 vs 21 vs 10		6.6 vs 5.0 vs 5.6		16
MTX vs MTX + 5-FU	48	S, R	25 vs 58		6.2 vs 8.1		80
CDDP vs CDDP + vincristine + MTX + B	209	S, R	15 vs 30	No significant difference	No significant difference	CDDP arm much better tolerated	81
CDDP vs MTX vs CDDP + MTX vs CDDP + 5-FU	200	S, R	14 vs 6 vs 12 vs 11		7.2 vs 4.0 vs 5.0 vs 5.0 (from graph)	CDDP superior to MTX OS; $P=.025$	29
CDDP + 5-FU vs CDDP + 5-FU + B + MTX	62	S, R	38 vs 61	FFS, 2.3 vs 4.5	7.8, no significant difference in arms	Underpowered study	82
CDDP vs CDDP + 5-FU vs CABO	382	S, R	15 vs 31 vs 34	TTP, 3 vs 4.3 vs 4.8	6.7, no significant difference in arms	TTP significant only for CDDP vs other arms	83
MTX vs edatrexate	264	S, R	16 vs 21	TTP, 6.4 vs 6.1			84
MTX vs nolatrexed	139	S, R, C	11 vs 3	TTP, 11.5 vs 1.9			85
CDDP + 5-FU vs CDDP + T	218	S, R	27 vs 26		8.7 vs 8.1	More high-grade AEs with CDDP + 5-FU	34
MTX vs gefitinib (500) vs gefitinib (250)	486	Prior platinum or ineligible for platinum	3.9 vs 7.6 vs 2.7		6.7 vs 6.0 vs 5.6	In platinum-naïve patients, MTX OS superior to gefitinib; HRs 1.5 and 1.6	30
Zalutumumab vs BSC	286	S, R, C, (all prior platinum)	6.3 vs 1.1	2.3 vs 1.9	6.7 vs 5.2	6% of controls used MTX	26

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; B, bleomycin; BSC, best supportive care; C, chemotherapy; CABO, cisplatin, methotrexate, bleomycin, and vincristine; CBCDA, carboplatin; CDDP, cisplatin; CTZ, cetuximab; D, docetaxel; FFS, failure-free survival; G, gemcitabine; HR, hazard ratio; L, liposomal doxorubicin; MTX, methotrexate; NA, not available; OS, overall survival; PB, cisplatin plus bleomycin; PD, progressive disease; PF, paclitaxel plus 5-FU; PFS, progression-free survival; TG, paclitaxel plus gemcitabine; TL, paclitaxel plus liposomal doxorubicin; R, radiation; RR, response rate; S, surgery; T, paclitaxel; TTP, time to progression.

*Bold signifies a statistically significant difference cited in manuscript.

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Table 2 Selected Randomized Trials (cont.)

Agents	N	Prior Treatments for Most	RR (%)	Median TTP or PFS (mo)	Median OS (mo)	Comments	Reference
Afatinib vs methotrexate	483	S, R, C (all platinum-exposed)	10 vs 6	2.6 vs 1.7	6.8 vs 6.0		95
Afatinib v CTZ	121	S, R, C (all platinum refractory)	8.1 vs 9.7 by central review	NA	NA	Investigator response assessments, 16.1 vs 6.5	86
CDDP vs CDDP + 5-FU vs 5-FU	249		17 vs 32 vs 13	TTP, 2.0 vs 2.4 vs 1.7	5.7, no difference among arms	Significant difference, combination vs single-drug arms	31
CDDP vs CDDP + 5-FU + CTZ	442	S, R, 38% prior C	20 vs 36	3.3 vs 5.6	7.4 vs 10.1	CDDP + 5-FU +/- CTZ x 6 then CTZ indefinitely until PD	8
CDDP vs CDDP + CTZ	117	S, R	10 vs 26	2.7 vs 4.2	8.0 vs 9.2	HR for OS same as Ref. 8	35
CDDP + 5-FU vs CDDP + 5-FU + panitumumab	657	S, R, 81% prior C	26 vs 37	4.6 vs 5.8	9.0 vs 11.1	OS, PFS improvement in p16-negative subset	36
D vs D + gefitinib	270	S, R, C	6 vs 13	2.1 vs 3.5	6.0 vs 7.3		87
D vs D + vandetanib	29	R, C	7 vs 13	0.8 vs 2.1	6.4 vs 5.7	Closed early for futility	88
T + G vs T + L	166	S, R, no C	20 vs 29	4.4 vs 6.0	8.6 vs 11.5	Total treatment cost: TG, \$10,295; TL, \$15,358	39

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; B, bleomycin; BSC, best supportive care; C, chemotherapy; CABO, cisplatin, methotrexate, bleomycin, and vincristine; CBCDA, carboplatin; CDDP, cisplatin; CTZ, cetuximab; D, docetaxel; FFS, failure-free survival; G, gemcitabine; HR, hazard ratio; L, liposomal doxorubicin; MTX, methotrexate; NA, not available; OS, overall survival; PB, cisplatin plus bleomycin; PD, progressive disease; PF, paclitaxel plus 5-FU; PFS, progression-free survival; TG, paclitaxel plus gemcitabine; TL, paclitaxel plus liposomal doxorubicin; R, radiation; RR, response rate; S, surgery; T, paclitaxel; TTP, time to progression.
*Bold signifies a statistically significant difference cited in manuscript.

event rates, but when PF was compared with PT, substantially more high-grade adverse events occurred in the PF arm.^{29,34} Therefore, the choice among these doublets should be based on patient-specific characteristics related to the adverse event profiles, such as hearing and kidney function and factors such as cost and complexity of treatment administration and supportive care.

Only one trial of multiagent chemotherapy has demonstrated statistically significant survival superiority versus another multiagent regimen in recurrent and/or metastatic SCCHN. In the EXTREME study, Vermorken et al⁸ randomized 442 patients in the first-line recurrent setting to either PF or PF plus cetuximab (PFC). The platinum agent used was either cisplatin or carboplatin, based on investigator choice. All patients received up to 6 cycles of PF or PFC. Patients continued indefinitely on cetuximab until disease progression. A statistically significant improvement was

seen in response rates (20% vs 36%), median PFS (3.3 vs 5.6 months), and median OS (7.4 vs 10.1 months), favoring the PFC arm. Adverse event profiles suggested that the addition of cetuximab was tolerable. These positive data are supported by a small randomized phase II study of cisplatin versus cisplatin plus cetuximab, which demonstrated similar hazard ratios favoring the addition of cetuximab to cisplatin but was not powered to demonstrate an OS difference.³⁵ However, how generalizable these results are for EGFR inhibitors in combination with cisplatin is unclear. A subsequent 657-patient study (SPECTRUM) investigating the addition of panitumumab to a chemotherapy backbone of PF demonstrated improvement in RR and PFS, but not OS.³⁶ Whether the outcome differences between EXTREME and SPECTRUM were because the anti-EGFR monoclonal antibodies had a different effect or were due to differences in the clinical trial designs is unclear. More patients in the SPECTRUM

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Table 3 Selected Trials of Combination Therapy

Agents	N	Prior Treatment	RR (%)	Median PFS or TTP (mo)	Median OS (mo)	Comments	Reference
Docetaxel + cetuximab	84	S, R, C (100% prior platinum)	11	3.1	6.7		89
Paclitaxel + cetuximab	46	S, R	54	4.2	8.1	No prior palliative treatment	37
Cisplatin + docetaxel	58	S, R	24	5.6	8.7	No prior palliative treatment	90
Cisplatin + docetaxel	30	S, R, C	17	TTP, 3.5	9.2	Both administered weekly	91
Cisplatin + paclitaxel	36	S, R	41	TTP, 5.0	11.0	Cisplatin, 75 mg/m ² Paclitaxel, 175 mg/m ² q21d	92
Docetaxel + carboplatin	68	S, R, no prior platinum	25	PFS, 3.8	7.4 mo		93
Paclitaxel + carboplatin	31	S, R, C (65%)	52	PFS, 5.4	12.8	Paclitaxel, 80 mg/m ² Carboplatin, AUC of 2 mg/mL/min, both weekly	94

Abbreviations: AUC, area under the curve; C, chemotherapy; OS, overall survival; PFS, progression-free survival; R, radiation; RR, response rate; S, surgery; TTP, time to progression.

study had chemotherapy exposure before enrollment (81% vs 38%), and the use of the anti-EGFR agent after chemotherapy completion was mandated in the EXTREME study but optional in SPECTRUM.

Whether the benefit seen with the addition of cetuximab to chemotherapy is platinum-specific is unknown. In a recent uncontrolled phase II study of paclitaxel and cetuximab in patients with prior platinum exposure, Hitt et al³⁷ reported a 54% RR with a median OS of 8 months. Although this uncontrolled study does not prove that the clinical benefit of cetuximab in combination can be extended to nonplatinum regimens, this atypically high RR suggests that this question should be prioritized for subsequent trials. In regard to the EXTREME and SPECTRUM trials and their use of 5-FU as part of the backbone control regimen, it is also worth noting that taxanes were not approved for this indication in Belgium at the time EXTREME was conducted (J. Vermorken, personal communication). In the United States, the combination of PT plus cetuximab, therefore, although not formally studied or sanctioned by the FDA, is often substituted for PF plus cetuximab because of easier administration and the perceived better adverse event profile of PT.

Cost-Effectiveness

Because only one trial has demonstrated modest (2.7 months) survival improvement with the use of

chemotherapy in the recurrent, metastatic setting, clinicians should consider other factors, such as the regimen's adverse event profile, patient convenience, and cost to the patient. Table 4 summarizes typical wholesale drug prices for 28 days of treatment based on the agents most commonly used in the United States, demonstrating a remarkable range from a low of \$11 for methotrexate to a high of \$12,227 for cetuximab. Using these estimates, drug cost alone for PF plus cetuximab for 6 cycles of treatment would be \$74,328 for a typical patient and \$95,796 if docetaxel were used instead of 5-FU in this combination.

Overall costs are difficult to compare when so few large randomized trials have been performed, but some reports of randomized clinical trials have incorporated cost into the data analysis. An early randomized clinical trial comparing methotrexate with a combination of cisplatin, vincristine, and bleomycin (COB) found that costs associated with one cycle of treatment were 4.3 times higher with COB despite no difference in response or survival rates.³⁸ Although this analysis only included costs of administration, subsequent attempts at cost and efficacy analysis have become more sophisticated. Fountzilaset al³⁹ performed a cost analysis of paclitaxel and gemcitabine versus paclitaxel plus pegylated liposomal doxorubicin in the first-line treatment of recurrent and/or metastatic SCCHN and found that the latter arm was more costly by 3649 EU (\$5042)

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Table 4 Price of 1-Month (28-Day) Supply of Drug for Typical Palliative Chemotherapy Regimens for Recurrent and/or Metastatic Squamous Cell Carcinoma^a

Drug	Typical Regimen	Dosing	Total Monthly Dose (mg)	Cost per mg (USD)	Total Drug Price for Example Patient (USD)
Cisplatin IV	Cisplatin and 5-FU q28d	100 mg/m ²	200	\$0.43	\$87
Carboplatin IV	Carboplatin and 5-FU q28d	AUC of 6 mg/mL/min	619	\$0.20	\$123
Docetaxel IV	Docetaxel q21d	75 mg/m ²	200	\$18.26	\$3,652
Paclitaxel IV	Cisplatin and paclitaxel q21d	175 mg/m ²	467	\$0.67	\$314
5-FU IV	Cisplatin and 5-FU q28d	1000 mg/m ² /d x 4 d	8000	\$0.01	\$74
Capecitabine PO	Capecitabine bid x 14 d then off x 7 d	1000 mg/m ² bid (4 tablets, 500 mg each)	150 tablets	\$39.88 ^b	\$5,982
Methotrexate IV	Methotrexate q7d IV	40 mg/m ²	240	\$0.05	\$11
Cetuximab IV	Cisplatin, 5-FU with weekly cetuximab	250 mg/m ²	2000	\$6.11	\$12,227

Prices from Lexicomp as of 4/22/2014: Pricing (Medi-Span): the pricing data provided represent the median average wholesale price (AWP) and/or average of AWP price for brand and/or generic product, respectively.
Abbreviations: 5-FU, 5-fluorouracil; AUC, area under the curve; IV, intravenous; PO, by mouth.
^aBased on a 6-foot-tall, 165-lb, 60-year-old man with a body surface area of 2 m² and a serum creatinine level of 1 mg/dL, AUC using the Cockcroft-Gault formula.
^bCost per 500-mg tablet.
Data from Lexicomp Online. Available at: https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7270. Accessed April 22, 2014.

when including all treatment and adverse event–related expenses despite no survival difference. More recently, 2 groups of investigators have attempted to evaluate the cost per life year gained and quality-adjusted life year (QALY) gained from the addition of cetuximab to the backbone of cisplatin and 5-FU based on the results of the EXTREME study.^{40,41} They found that the incremental cost-effectiveness was 92,226 GBP (\$154,919) for each life year gained and 121,367 GBP (\$203,879) per QALY. They concluded that the use of cetuximab in this setting was not cost-effective and not recommended because the costs were substantially higher than those normally acceptable to the British National Health Service.

Biomarkers as Predictors of Clinical Benefit

The past decade has seen major advances in the treatment of several cancers through the

use of predictive biomarkers, such as HER2/neu overexpression as a predictor of response to trastuzumab in breast cancer, and EGFR mutation as a predictor of response to erlotinib in non–small cell lung cancer. Although there are markers and panels of markers that, when evaluated over the treatment and follow-up interval, can predict therapeutic responses in patients with SCCHN,^{42–45} no markers yet exist that have robustly demonstrated utility in terms of chemotherapy selection. Examples of candidates for these biomarkers include ERCC1 protein or mRNA levels as predictors of resistance to platinum compounds, but the data are inconsistent and antibody reagents for ERCC1 have been problematic.^{46,47} Thymidine synthase (TS) and thymidine phosphorylase (TP) have been investigated as potential markers of 5-FU benefit without conclusive or consistent results.⁴⁸

More recently, a shift has occurred from biochemical-based to genetics-based assays, and

even whole-genome sequencing is advocated by some as a rational and often “actionable” approach to drug benefit prediction. As discussed, although a few examples exist in which genetic alterations have proved useful in other cancers, no validated markers exist for selecting among treatment choices for recurrent and/or metastatic SCCHN. Most genetic alterations in SCCHN are loss of function of tumor suppressor genes in the TP53, CDKN2A, and PTEN pathways. These alterations are not presently easily targetable by drugs, because restoring function as an anticancer strategy has not yet been possible.⁴⁹ Similarly, for the recently discovered NOTCH1-inactivating mutations in SCCHN ($\approx 12\%$ – 19%), no specific therapy exists to restore function.^{49–51} Claims that up to 80% of oral cavity squamous cell carcinoma have targetable genetic alterations, for example, are based on biological plausibility concerning agents against these targets, rather than clinical demonstration of efficacy.^{52,53} Emerging targets of interest include FGFR, HER2, MET, PI3K, and mTOR, but the promise of benefit from inhibiting these targets has yet to be realized.^{54,55} Despite the large amount of advertising for the use of these genomic and genetic screening assays, reported improvements in outcome are limited to a small minority of highly selected patients. Therefore, use of these assays to determine treatment should be limited to the context of experimental treatment. Widespread ad hoc use should be discouraged.

Over the past decade it has become clear that HPV-related oropharyngeal squamous cell carcinomas are a clinically unique subset of SCCHN, with a much better prognosis. Results of the SPECTRUM trial, using p16 immunohistochemistry as a surrogate for HPV, suggest that for panitumumab, benefit may be limited to the p16-negative patients, but a retrospective evaluation of a subset of patients in the EXTREME trial demonstrated no association between p16 or HPV and OS or PFS benefit for cetuximab.^{36,56} Therefore, although p16/HPV seems to be prognostic in recurrent and/or metastatic SCCHN, data do not yet support a benefit prediction role for p16/HPV in this population with respect to systemic therapy treatment, and the data are conflicting for anti-EGFR1 monoclonal antibodies.

Practical Treatment Advice

Single Agents

Methotrexate and paclitaxel are appropriate initial single-agent choices for patients with recurrent and/or metastatic SCCHN. These agents have the advantage of good patient tolerability, have well-established track records of relevant anticancer activity, and are not overly burdensome in terms of administration. 5-FU is also an appropriate agent, but the need for continuous infusion is a significant burden for many patients. Capecitabine, cetuximab, and docetaxel also have reasonable anticancer activity; however, their high cost precludes their recommendation over much less expensive choices. This approach is favored especially after early relapse from cisplatin-based chemoradiation treatment, when rechallenge with a platinum is unlikely to be beneficial. The taxanes can be dosed either on a weekly or every-21-day schedule, but the weekly schedule has the advantage of better tolerability and less irrevocable toxicity per dose, so the clinician has the option to modify dosing more frequently based on patient tolerability issues. Table 5 lists recommended doses and schedules of administration. It is common, especially in pretreated patients, to hold taxane dosing every few weeks on an as-needed basis because of cumulative bone marrow toxicity. Cisplatin and carboplatin are generally not used as single agents. Cisplatin especially has a worse adverse event profile than the agents listed earlier and therefore, without convincing evidence of superiority versus methotrexate or the taxanes, should not be used alone.

Multiagent Treatment

For patients with good performance status and appropriate organ function (ie, renal, hepatic) with rapidly progressive or symptomatic disease, triple-agent treatment with PFC or PT plus cetuximab (PTC) (Table 5) may be appropriate, but one must balance the markedly increased adverse event profile and cost of these multidrug combinations against the promise of modest median OS extension. Many favor PTC over PFC because of its better tolerability and the infusion pump requirement with 5-FU, despite the fact that a taxane triplet has not been evaluated in a phase II study and therefore is not supported by level 1 evidence per the NCCN Clinical Practice Guidelines in Oncology for Head and Neck Cancers.⁵⁷

Table 5 Commonly Used Systemic Treatment Options for Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma

Regimen	Dose	Schedule
Methotrexate	40–60 mg/m ² IV	Weekly indefinitely
Paclitaxel	80–90 mg/m ² IV	Weekly indefinitely
Docetaxel	25–30 mg/m ² IV	Weekly indefinitely
PFC		
Cisplatin or carboplatin	Cisplatin, 100 mg/m ² IV; carboplatin, AUC of 5 mg/mL/min IV day 1	q21d x 6
5-FU	5-FU, 1000 mg/m ² /d x 4 d IVCI days 1–4	q21d x 6
Cetuximab	Cetuximab, 400 mg/m ² IV day 1, then 250 mg/m ² IV	Weekly indefinitely
PTC		
Cisplatin	Cisplatin, 75 mg/m ² IV day 1	q21d
Paclitaxel	Paclitaxel, 75 mg/m ² IV day 1	q21d
Cetuximab	Cetuximab, 400 mg/m ² IV day 1, then 250 mg/m ² IV	Weekly indefinitely

Abbreviations: 5-FU, 5-fluorouracil; AUC, area under the curve; IV, intravenous; IVCI, intravenous continuous infusion; PFC, cisplatin/carboplatin, 5-FU, cetuximab; PTC, cisplatin, paclitaxel, cetuximab.

Finally, although many patients benefit from these standard treatments, knowledge remains limited because so few definitive adequately powered studies have been performed. Patients and clinicians should be encouraged to participate both in trials of new promising experimental agents and in trials whose purpose is to better define the role of currently available treatments.

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