Chapter 9
Management of Widely Metastatic and Unresectable Cutaneous Squamous Cell Carcinoma

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Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer and though most cases are easily cured with surgical excision, it is associated with a 3 % metastatic risk [1, 2]. Seventy to 80 % of all non-melanoma skin cancers occur in the sun exposed regions of the head and neck. It is estimated that 2500–8800 patients succumb each year to CSCC in the United States, often a result of uncontrolled loco-regional disease [3, 4]. Distant metastases are less common. This chapter will discuss the management of such patients with unresectable local, regional, or distant disease, particularly with regard to chemotherapy and chemoradiation. Radiation therapy for nodal disease is also discussed in Chap. 8.

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Clinical Features

Location of Metastatic Spread

Risk factors of primary tumors and patient factors which impact risk of metastasis are covered extensively in earlier chapters of this book. However, it is important to note that up to 27 % of patients with nodal metastases have no identifiable primary lesion on cutaneous skin examination [5]. This may be because most patients with metastatic CSCC have had multiple primary CSCC tumors and determining which primary gave rise to metastases can sometimes prove difficult. Studies to date have relied upon tumors' anatomic proximity to metastatic nodal basins, high-risk features, and timeframe of primary tumor appearance to metastasis to determine which of several primary tumors give rise to nodal disease. However, such information may be imprecise. Genetic profiling of primary tumors and metastases may prove very helpful in future investigations to clarify which tumors result in metastases.

Cervical lymph nodes are the most common site of metastatic spread from CSCC (60 %, often involving the submental or submandibular nodes), followed by the parotid gland (30 %). CSCC of the pinna, given its regional lymphatic drainage pattern and proximity to the parotid gland, most often (60–70 %) results in metastatic disease to the ipsilateral cervical lymph nodes or parotid gland [6]. Ear location may carry a higher risk of metastasis [7]. Fewer than 20 % of patients with metastasis present with distant metastases at the time of initial presentation. Half of patients develop recurrence at the primary cutaneous site prior to the development of metastatic disease [8]. Thus, patients who develop locally recurrent CSCC after clear-margin excision (Mohs or non-Mohs) should be considered at risk for metastasis.

Staging Systems for Metastatic CSCC

Traditionally, TNM staging for CSCC categorized lymph node metastases as either involved or uninvolved; however, the seventh edition of the American Joint Committee on Cancer (AJCC) staging system for CSCC revised the nodal staging system to reflect the number, diameter, and laterality of involved lymph nodes (Table 9.1) [9]. While this is an improvement over the former TNM staging system, contralateral metastases only occurred in 2 % of patients and there was only a 1 % difference in the risk of death at 3 years in the N2 subgroups in one study [10]. Others have proposed alternatives to AJCC nodal staging (Table 9.2). O'Brien et al. developed a staging system for metastatic CSCC of the head and neck that separates parotid and neck disease. The staging system when applied to 87 patients trended toward a significant correlation between survival and P stage ($p=0.07$). Increasing clinical ($p=0.04$) and pathologic ($p=0.006$) N stage was associated with decreased survival. O'Brien's staging system is an improvement over the TNM, but is complex due to the separation of the parotid and neck staging systems and the utility of such separation has not been investigated [12].

Table 9.1 AJCC Regional Lymph Node Staging for CSCC [9]

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest diameter
N2a	Metastasis in a single ipsilateral node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

Table 9.2 Proposed alternative staging systems for patients with metastatic cutaneous squamous cell carcinoma

O'Brien et al. (2002) [11]	Forest et al. (2010) (N1S3) [12]
Parotid gland	
P1: Node ≤3 cm	I: Single lymph node measuring ≤3 cm
P2: Node >3 cm but ≤6 cm or multiple nodes	II: Single lymph node measuring ≤3 cm or multiple lymph nodes measuring ≤3 cm
P3: Node >6 cm or facial nerve involvement, skull base invasion	III: Multiple lymph nodes measuring >3 cm
Neck	
N0: Clinically negative neck	
N1: Single node ≤3 cm (ipsilateral)	
N2: Single node >3 cm, multiple or contralateral nodes	

Forest et al. developed the N1S3 staging system, which considers nodes from the parotid and neck together [12]. This system defines three stages based on the number of involved nodes from the parotid and neck and size above or below 3 cm. The N1S3 system was developed based on a 215 patient cohort and then applied to a different 250 patient cohort for validation. This staging system was able to discriminate between the three different groups for locoregional control (log rank $p=0.01$) and disease-specific survival ($p=0.004$) [12].

Treatment and Prognosis

Nodal Metastases

A thorough discussion of management of nodal metastases and recent data in this realm is the subject of Chap. 8. Some have advocated for elective lymph node dissections in patients with high risk lesions greater than 4 cm, cartilage invasion, deep invasion, or high risk lip lesions, but data are limited [13]. There is currently no formal consensus as to the appropriate treatment strategy for patients with nodally metastatic

CSCC, but patients should be treated with the intent of cure. Patients are generally offered either lymphadenectomy or radiation treatment, or a combination of both.

Induction and Definitive Chemotherapy for Advanced CSCC

Due to the rarity of the diagnosis of metastatic CSCC, the literature for chemotherapy is limited to small phase II studies and case series, which are summarized in Table 9.3 [14, 19]. There are no FDA-approved chemotherapy drugs specifically for

Table 9.3 Summary of trials utilizing systemic chemotherapy to treat cutaneous squamous cell carcinoma

Authors	Study design, n	Treatment	Response	Notes
Traditional definitive chemotherapy				
Guthrie et al. (1990) [14]	Cohort, 28 Advanced (BCC and SCC)	Cisplatin and Doxorubicin, Cisplatin (includes both neoadjuvant and definitive cases)	28 % CR 40 % PR	
Sadek et al. (1990) [15]	Phase II, 14 Advanced	Cisplatin, 5-FU, bleomycin and infusional 5-FU	84 % ORR 30 % CR 34 % PR	
Khansur et al. (1991) [16]	Case series, 7 Metastatic or locally advanced	Cisplatin and 5-FU	3 CRs 3 PRs	One patient was alive and disease-free at 2 years
Wollina et al. (2005) [17]	Case series, 4 Advanced	Capecitabine and Interferon	2 CR 2 PR	
Nakamura et al. (2013) [18]	Case series, 8 Metastatic	Cisplatin and Adriamycin, Cisplatin and Epirubicin, Carboplatin and Adriamyycin	2 CR 1 PR 2 SD 3 PD	
Adjuvant and neoadjuvant chemotherapy				
Guthrie et al. (1990) [14]	Cohort, 28 Advanced (BCC and SCC)	Cisplatin and Doxorubicin, Cisplatin (includes both neoadjuvant and definitive cases)	28 % CR 40 % PR	
Denic (1999) [19]	Case series, 5 Advanced (BCC or SCC)	Neoadjuvant Cisplatin and Bleomycin	1 CCR 3 PR 1 PD	
Tanvetyanon et al. (2015) [30]	Retrospective cohort study, 61 Stage III/IV	Surgery + Radiation vs. Surgery + Chemoradiation	Chemo-XRT: 2 DM 8 LR XRT: 1 DM 13 LR	HR of chemo-XRT:XRT = 0.31 (95 % CI, 0.13–0.78) for risk of disease recurrence or death

(continued)

Table 9.3 (continued)

Authors	Study design, n	Treatment	Response	Notes
Targeted therapy (definitive unless otherwise stated)				
Read (2007) [20]	Case series, 3	Erlotinib	2 PR	Tumor recurred on discontinuation in the CR patient
	Metastatic or locally recurrent		1 CR	
Maubec et al. (2010) [21]	Phase II, 36	Cetuximab	69 % ORR	Infusion reactions and acneiform rash notable
	Metastatic		2 CR	
			8 PR	
Giacchero et al. (2011) [22]	Case series, 8	Cetuximab, Cetuximab and Radiotherapy	3 CR	Grade 3 or 4 adverse events in eight patients
	Advanced or unsectable		3 PD	
			1 SD	
			1 PD	
Kalapurakal et al. (2012) [23]	Case series, 4	Cetuximab	3 CR	One CR relapsed within 6 months
	Recurrent SCC		1 PR	
Lewis et al. (2012) [24]	Phase II, 23	Neoadjuvant Gefitinib	18.2 % CR	
	locally advanced		27.3 % PR	
O'Bryan et al. (2013) [25]	Case series, 7 high risk post resection	Six patients received cetuximab + surgery	4 CR	
		One patient received cetuximab + surgery + XRT	2 PD	
			1 UA	
Preneau et al. (2013) [26]	Pilot study, 19	Five patients received cetuximab + XRT	9 PR	
	Inoperable	Nine patients received cetuximab + carboplatin	6 SD	
			4 PD	
		Five patients received cetuximab monotherapy	47 % ORR	
			78 % overall disease control	
Heath et al. (2013) [27]	Phase I, 15 locally advanced or lymph node involvement	Erlotinib + XRT	65 % OS (2 years)	
			60 % DFS	
			26.7 % recurrence	

CR complete remission, *PR* partial remission, *CCR* complete clinical remission, *ORR* overall response rate, *OS* overall survival, *SD* stable disease, *PD* progression of disease, *PFS* progression free survival, *DM* distant metastasis, *LR* local recurrence, *UA* unable to access response, *DFS* disease free survival

CSCC and no well-established treatment regimens. Thus the information below is for off-label uses. Most regimens have been based on mucosal head and neck SCC treatment protocols.

Advanced CSCC, defined as loco-regional disease that has failed surgery and radiation or is widely metastatic, is generally treated with systemic chemotherapy.

Previously chemotherapy was used primarily as a palliative treatment, but current regimens are implemented with curative intent for loco-regional disease. Conversely, treatment of distant organ metastases and intracranial extension remains mostly palliative. It is important to recognize that many chemotherapeutic regimens are associated with significant toxicity.

Induction chemotherapy is the administration of chemotherapy prior to definitive loco-regional control. It is beneficial for unresectable tumors (that may be resectable after induction therapy) or for early treatment of subclinical metastases. Induction chemotherapy is generally used in conjunction with radiation. The most frequently used induction chemotherapy regimens are 5-fluorouracil (5-FU)/cisplatin combinations [28].

Definitive chemotherapy, in contrast to induction therapy, is aimed at cure or best possible control of disease not amenable to surgical clearance. It is usually combined with radiation and is most often used for organ preservation or for patients unable to tolerate surgery. The most common definitive chemotherapy regimens include cisplatin, 5-FU/cisplatin combinations, 5-FU/carboplatin combinations, and paclitaxel/carboplatin combinations [28]. Most studies evaluating these regimens have been performed in mucosal head and neck SCCs (originating from the oral cavity, oropharynx, hypopharynx, and larynx). Pignon et al. [29] published a large meta-analysis of 87 randomized trials of mostly mucosal (non-cutaneous) head and neck SCCs, which included 16,485 patients. Their analyses found greater benefit of chemotherapy administered concurrent with radiation (HR 0.81, 95 % CI 0.79–0.86) as compared to induction chemotherapy administered prior to radiation and/or surgery which did not show a survival advantage (HR 0.96, 95 % CI 0.9–1.02) [29].

Studies specific to CSCC are limited and much work remains to define optimal systemic therapy. Though most patients will have an initial clinical response, sustained remissions are rare and the large majority of patients ultimately succumb to disease. Studies of traditional chemotherapy have focused on definitive rather than induction regimens. Khansur et al. [16] reported a case series of seven patients with advanced locoregional or metastatic CSCC treated with cisplatin and 5-FU. This series noted three partial responses, three complete responses, and one stable disease. Sadek et al. [15] reported an 84 % objective response to a combination regimen of cisplatin, 5-FU, and bleomycin in 13 patients with CSCC. Complete response was seen in 30 % of patients. Nakamura et al. [18] more recently reported a complete response in two out of eight patients receiving a combination of platinum and anthracycline chemotherapy with progression of disease in three patients.

There are a few case series that evaluate alternatives to platinum based chemotherapy. Wollina et al. [17] performed a prospective case series of four patients with advanced CSCC treated with oral capecitabine plus subcutaneous interferon alpha, of which two patients had complete response and two a partial response. Of note, the patients had only mild side effects.

Adjuvant Chemotherapy

Adjuvant chemotherapy is generally used in conjunction with adjuvant radiation postoperatively after clear surgical margins have been obtained for patients with high-risk pathologic features or history of recurrence for whom concern for further recurrence and metastasis is high. Identification of patients eligible for adjuvant chemotherapy is made case by case since no established standards are in place to guide patient selection.

Similar to the definitive chemotherapy regimens, utilization of adjuvant chemotherapy following definitive surgical excision is primarily extrapolated from the head and neck literature. To our knowledge, there is one study in the literature that specifically evaluates adjuvant chemoradiation for CSCCs. Tanvetyanon et al. [30] retrospectively compared 61 patients who underwent definitive surgical excision followed by adjuvant radiation or chemoradiation. This series noted a decreased risk of recurrence and death on multivariate analysis in patients who received chemoradiation compared to those who only underwent adjuvant radiation (HR 0.31, 95 % CI 0.13–0.78). These results indicate that treating high-risk patients post surgery with adjuvant chemoradiation, prior to the occurrence of clinical metastases, may result in a higher cure rates and prevention of mortality. However, defining which patients are candidates for adjuvant chemoradiation requires further study.

A significant amount of research has investigated the use of retinoids in the management of CSCC lesions, but while they offer some prophylactic benefit, they do not alter the progression of the existing tumor [31]. Their prophylactic use is covered more extensively in Chap. 5.

Molecular Targeted Therapies

Currently there are no available molecular markers to identify high-risk CSCC patients or to aid treatment selection for those with metastatic disease. However, since CSCC is among the most heavily mutated of all cancers [32], it is likely that therapies targeting specific genetic and molecular alterations within a given CSCC will play a pivotal role in future therapeutic approaches. As the mutational landscape of CSCC appears to be highly variable from one tumor to the next without a predominating defect (in contrast to the hedgehog pathway in basal cell carcinoma or bRAF in melanoma), optimal molecular therapy for CSCC may need to be highly individualized [33]. The epidermal growth factor receptor (EGFR)-Ras-Raf-MEK-ERK signaling pathway has been implicated in head and neck SCCs [34]. Therapeutics that specifically target this pathway have recently been studied in patients with CSCC.

Cetuximab (Erbitux) is a human-mouse chimeric monoclonal antibody that competitively binds to the external domain of the EGFR, thereby inhibiting dimerization and overall tumor growth. It is currently approved as adjuvant therapy with concomitant radiation for use in patients with metastatic mucosal head and neck

SCC. A recent phase II trial investigated the use of cetuximab in metastatic CSCC. After 6-weeks of treatment, there was a 69 % disease response rate in the 31 patients in the study. Mean progression-free and overall survival were 121 and 246 days, respectively [21]. Interestingly, the development of an acneiform drug rash with treatment was associated with better outcomes, as noted in prior studies in head and neck cancer patients. In a small case series, cetuximab alone or in combination with radiation was shown to be efficacious with a treatment response in six out of eight patients [22]. A phase II study of neoadjuvant gefitinib which inhibits the ATP-binding site of EGFR showed an 18 % complete response and 27 % partial response in 22 subjects [24]. Two-year overall, disease-specific, and progression-free survival rates were 72.1 %, 72.1 %, and 63.6 %, respectively. Some data have demonstrated similar benefits with erlotinib, currently approved for use in non-small cell lung cancer [20, 27]. Additional studies of EGFR antagonists alone or in combination with radiation and as adjuvant and neoadjuvant treatment for locally extensive and metastatic CSCCs are needed given the current dearth of literature.

The hedgehog (Hh) pathway is a developmental signaling pathway involved in numerous cellular processes, affecting cell survival and differentiation. Mutations via ligand-independent mechanisms of constitutive activation have been noted in cancers such as basal cell carcinoma. Preliminary reports in murine models have demonstrated that overexpression of PTCH-1 (a regulatory tumor suppressor acting through the Hh pathway) in transgenic mice synergizes with Hras mutations to promote SCC development [35]. These findings could have implications with regards to treatment utilizing novel Hh signaling inhibitors. However, anecdotally, cutaneous basosquamous carcinomas (a histologic mix of basal and squamous cell carcinoma) treated with Hh inhibitors do not do well. Though the basaloid component regresses, the squamous portion appears resistant and subsequently predominates. Thus, Hh inhibitor monotherapy may have a limited role in CSCC therapy.

Conclusion

Metastatic CSCC presents a management challenge due to lack of prognostic estimates and clinical trials. Combined surgical resection followed by adjuvant radiation is the current standard treatment for nodal disease. Chemotherapy is generally reserved for patients with recurrent local and/or nodal disease after such treatment, or for those with rare distant organ metastases. There are no clearly defined protocols for systemic therapy of CSCC. Though various regimens have been tried, no treatment has been reported to be highly effective. Early treatment with adjuvant chemoradiation immediately after surgical clearance shows promise but defining an appropriate patient population for adjuvant therapy and defining optimal regimens requires additional investigation. Targeted chemotherapy and immuno therapy are likely to play a major role in the future, but further studies are necessary to elucidate molecular markers for prognostication and to individualize therapy in this heavily mutated and genetically heterogeneous disease.

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