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The Role of Targeted Molecular Inhibitors in the Management of Advanced Nonmelanoma Skin Cancer

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Surgical treatment remains the standard of care for nonmelanoma skin cancer and is successful for the vast majority of patients with these tumors. The treatment of patients with metastatic or unresectable nonmelanoma skin cancer, however, has until recently been based solely on traditional methods of chemotherapy and radiation. However, these methods have high rates of treatment failure, morbidity, and mortality, and alternative treatment modalities for patients with aggressive or advanced disease are needed. As in other areas of cancer therapeutics, recent research elucidating the molecular basis of cancer development, and the subsequent arrival of targeted molecular inhibitors for cancer therapy, have been met with much excitement. In this review, we seek to illuminate recent developments and future possibilities in the use of targeted molecular inhibitors for treatment of advanced squamous cell carcinoma, basal cell carcinoma, and dermatofibrosarcoma protuberans.

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Squamous Cell Carcinoma

Most cutaneous squamous cell carcinomas (CSCCs) occur on the head, neck, and upper extremities.[1] Most of these tumors are cured after focused intervention, including cryotherapy, surgical excision, radiation therapy, or Mohs micrographic surgery. Unfortunately, locally advanced, aggressive, recurrent, or metastatic SCC, particularly of the head and neck, are much more difficult to treat. In patients with squamous cell carcinomas of the head and neck (SCCHN), including primary lip, oral cavity, nasal cavity, paranasal sinus, pharyngeal, and laryngeal tumors, local recurrence occurs in 50% of patients, resulting in a median overall survival of only 6-9 months.[2]

The primary targets of molecular inhibition in squamous cell carcinoma include the epidermal growth factor receptor (EGFR), the vascular endothelial growth factor (VEGF) and its receptor, and tyrosine kinase (TK). A small number of studies have shown that these molecules are overexpressed in a subset of CSCC and may be associated with more aggressive clinical behavior.[3-5] There has been much interest in targeted molecular inhibitors for SCCHN as an alternative or adjuvant measure to the current standard of care: radiation and platin-based chemotherapy, and these have been used with some success in this population of patients. Although clinical experience with use of these agents for advanced CSCC has thus far been limited, there is hope that these therapies may also be useful for patients with aggressive or advanced CSCC.

EGFR Inhibitors

Overexpression of the EGFR receptor is a dominant process in SCCHN. This can result in constitutive activation of intercellular TK, a trigger of multiple downstream phosphorylation cascades that lead to cell survival.[6] Studies have shown a relationship between EGFR gene copy number and poor clinical outcome.[7] Cisplatin and 5-fluorouracil (5-FU), 2 chemotherapeutic agents that are considered the standard of care in treatment of SCCHN, alter the expression of EGFR and its ability to phosphorylate TK. EGFR also plays a role in DNA repair systems after radiation-induced DNA damage. It was therefore hypothesized that the use of targeted EGFR inhibitors in combination with chemotherapy and radiation could enhance their antitumor effects.[7]

Cetuximab (Erbitux, ImClone Systems Incorporated, Branchburg, NJ) is a human-murine chimeric monoclonal antibody against EGFR. It has shown promise in the treat-

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ment of locally advanced, recurrent, or metastatic SCCHN and is the only targeted EGFR inhibitor to receive Food and Drug Administration approval for use in localized disease in combination with radiation. It has also gained approval for use as monotherapy in chemotherapy-resistant recurrent or metastatic SCCHN. It is important to note that cetuximab alone has yet to be compared with radiation plus chemotherapy in locally advanced disease.[7,8] One large study of 424 patients with locally advanced SCCHN randomized to treatment with radiation plus weekly infusions of cetuximab or radiotherapy alone had promising results. Those who received combination treatment showed a 74% overall response rate (ORR), compared with 64% ORR in patients who received radiotherapy alone ($P = 0.02$). Locoregional control rates were 24.4 months versus 14.9 months, respectively ($P = 0.005$), and overall survival was 49 versus 29.3 months ($P = 0.03$).[8,9]

Recent evidence has also shown the benefit of cetuximab when combined with platinum-based chemotherapy and 5-FU in patients with recurrent or metastatic SCCHN.[10] in a study by Vermorken et al,[9] 442 eligible patients with untreated recurrent or metastatic SCCHN were randomized to receive 5-FU with cisplatin or carboplatin, with or without cetuximab. The ORR was 36% versus 20% with and without cetuximab ($P = 0.001$). Survival increased from 7.4 to 10.1 months with the addition of cetuximab ($P = 0.04$), and progression-free survival increased from 3.3 to 5.6 months ($P \leq 0.0001$).

Other targeted EGFR inhibitors are also currently under investigation in clinical trials. Zalutumumab (Genmab, Utrecht, Netherlands) and Panitumumab (Vectibix, Amgen, Thousand Oaks, CA) are fully human monoclonal antibodies to EGFR. Zalutumumab is currently in a phase 1/2 study in combination with chemoradiation for first-line treatment of patients with advanced SCCHN. In addition, the Danish Head and Neck Cancer Group is preparing a phase 3 trial in which 600 previously untreated patients will be randomized to receive radiation alone or radiation plus zalutumumab.[11] Panitumumab is currently in a phase 2 trial comparing radiation and cisplatin to radiation and panitumumab, and is also in a phase 3 trial comparing radiation and cisplatin to radiation and panitumumab in patients with locally advanced stage III/IV SCCHN.[12]

Compared with established therapies, EGFR inhibitors are fairly well tolerated. Cutaneous side effects include hypertrichosis and a papulopustular acneiform eruption, which is dose-dependent, occurs predominantly on the head, neck and upper body, and arises in the first few weeks of therapy.[7,13] Importantly, this eruption does not limit treatment and is effectively controlled with traditional acne therapies.[14]

On the Horizon

VEGF is a proangiogenic cytokine with 4 isoforms (VEGFA-D) that can be secreted by tumor cells.[15] VEGF and its markers are associated with tumor progression, changes in microvessel density, and development of lymph node metastases in SCCHN.[9] Many targeted molecular therapies to VEGF and VEGF TKs have proven efficacy in other malignancies, and research into their use for SCCHN is growing.

Bevacicumab (Avastin, Genentech, South San Francisco, CA) is a fully human monoclonal antibody against VEGF, currently used in the treatment of colon, breast, renal, and other cancers. It is being tested for recurrent and metastatic SCCHN in a phase 3 trial comparing chemotherapy alone versus chemotherapy plus bevacizumab. In addition, in an ongoing phase 2 trial, cituximab, radiotherapy, and pemetrexed with or without bevacizumab is being tested in patients with locally advanced SCCHN.[16] There is hope that the combination of EGFR and VEGF pathway inhibitors will provide an increased clinical benefit in such patients.

Sorafenib (Nexavar, Onyx Pharmaceuticals, Emeryville Calif/Bayer Healthcare, Morristown, NJ) and sunitinib (Sutent, Pfizer, Inc, New York, NY) are TK inhibitors hypothesized to work by hindering tumor angiogenesis and cell proliferation.[16] They each inhibit multiple pathways, including VEGF and platelet-derived growth factor (PDGF). Sorafenib is currently in phase 2 trials, including one containing 88 patients with recurrent or metastatic SCCHN who are randomized to receive cetuximab with or without sorafenib.[17] Of note, there is increasing concern regarding the dermatologic side effects of sorafenib. Hand-foot syndrome, alopecia, and pruritus can be seen in a significant number of patients. More concerning, however, are the increasing reports of epithelial skin cancer growth, including SCC, keratoacanthoma-type SCC, and basal cell carcinoma (BCC), in patients treated with sorafenib for other indications. In many of these cases the skin cancers arose after sorafenib initiation, sometimes with rapid onset, and no new skin cancers were observed after treatment discontinuation.[9,18] Further research is certainly required to delineate these possible associations.

In a recent study, sunitinib monotherapy resulted in a 50% response rate in 38 patients with recurrent or metastatic SCCHN: one patient experienced partial response, 18 had stable disease, and 19 had progressive disease. These results were complicated, however, by a high rate of adverse events, including grade 3-5 tumor bleeding (a known complication in angiogenesis inhibitors) in 18% of patients.[10,19]

In summary, although the vast majority of studies focus on the use of molecular inhibitors in SCCHN, and more research is certainly needed, there is reason for optimism about these new treatment modalities and their emerging role in treating patients with advanced or aggressive CSCC.

Basal Cell Carcinoma

Targeted molecular therapy for basal cell carcinoma has focused mostly on the Hedgehog signaling pathway (SHH). PTCH, a multitransmembrane protein member of the patched gene family, is a receptor important for its inhibition of smoothened (SMO), a protein that activates Gli and results in downstream target gene transcription. Sonic Hedgehog protein functions early in the pathway to bind PTCH, blocking its inhibitory effect on SMO. This pathway plays a crucial role in normal cell development, replication, and differenti-

ation, as well as hair growth. Its dysregulation is implicated in the development of BCC, medulloblastoma, and pancreatic carcinoma. In addition, mutations in PTCH that result in continuous smoothened activation are the most common alterations found in BCC, followed by mutations in p53 and CDKN2A.[11,20] PTCH gene mutations are also found in patients with basal cell nevus syndrome (BCNS).

As in CSCC, most BCCs are adequately controlled with focused, often surgical, intervention. When the burden of disease increases, however, as in patients with inoperable tumors, or innumerable BCCs not amenable to surgery, treatment options are few. As a result, the development of targeted molecular therapy for BCC has been met with considerable excitement. Many naturally occurring and synthetic agents have been found to inhibit the SHH.[12,21,22] Only a few, however, are being studied for clinical use.

GDC-0449

GDC-0449 (Genentech, South San Francisco, CA), a small molecule inhibitor of SMO, is the most widely characterized of the SHH inhibitors. In a recently reported phase 1 study, 33 patients with BCCs that could not be treated with surgery, radiation, or other systemic therapy received varying doses of the drug. Eighteen of 33 patients had an objective response on the basis of imaging, physical examination, or both. There were 2 complete responders, and 16 partial responders, defined as a 50% reduction in palpable or visible tumor.[13,23]

A case report of the use of GDC-0449 in one patient with BCNS was similarly encouraging. A 53-year-old man with a history of at least 750 surgically treated BCCs, including one metastatic to his right superior inguinal groin requiring lymph node dissection and radiation, was given an oral dose of 270 mg/d after he showed repeated reluctance to further surgical intervention. After eight weeks of treatment, a significant reduction in the size and number of BCCs was observed, and by 36 weeks, his BCCs had disappeared, excepting one 8-mm lesion of the conchal bowl. Of note, this patient did experience significant scalp, eyebrow, and eyelash alopecia as a side effect of treatment.[14,20] This agent has otherwise been well tolerated in early studies.

GDC-0449 is not a magic bullet, unfortunately. As noted previously, a variety of mutations can be found in sporadic BCCs, and SMO mutations that confer tumor resistance to the drug have been reported.[24] Nevertheless, much reason for optimism exists, particularly in the treatment of patients with BCNS. Phase 2 trials of the drug in BCNS are underway.[25] Further research will be needed to further refine treatment and overcome emerging methods of resistance.

On the Horizon

Many other agents that inhibit the SHH pathway are in various stages of development and testing. Robotnikinin is the first reported inhibitor of SHH Protein, which functions to bind to PTCH and remove its inhibition on SMO, allowing for constitutive cellular signaling. BMS 833-923 and IPI-926 are, like GDC-0449, inhibitors of SMO that are in development. GANT-58, GANT-61, and JK 184 are Gli inhibitors that work downstream from SMO to inhibit pathway signaling and could provide a method of treatment for patients with different mutations in SHH proteins, including those who develop resistance to SMO inhibitors.[15,26]

Dermatofibrosarcoma Protuberans

Surgical treatment remains the standard of care for dermatofibrosarcoma protuberans (DFSP). The treatment of metastatic or unresectable DFSP, previously unsatisfactory and largely unsuccessful, has fortunately been revolutionized in recent years. This revolution became possible with the characterization of a genetic abnormality seen in >90% of DFSP: the chromosomal translocation t(17;22). This translocation brings about the fusion of COL1A1 and PDGFB, resulting in an increase in PDGFB transcription, which acts as a stimulus for malignant transformation. This discovery led to the hypothesis that molecular inhibitors targeting PDGFR, already established in the treatment of other cancers, including leukemias and gastrointestinal stromal tumors, could be effective in blocking the effect of deregulated PDGFB expression in DFSP.[16,27]

Imatinib Mesylate

Imatinib Mesylate (IM, Gleevac, Novartis, Basel, Switzerland) is a small molecule kinase inhibitor of ABL, KIT, ARG, FMS, and PDGFR, which has shown encouraging results in the treatment of metastatic or unresectable DFSP. In a pooled analysis of two phase 2 clinical trials, 24 patients were treated with 400 mg or 800 mg daily, and responses to therapy were assessed at 14 or 16 weeks. Eleven patients (45.9%) showed a partial response, and 6 (25.0%) showed stable disease, for 70.9% (17/24 patients) achieving clinical benefit. Additionally, progression-free survival was 58% and median time to progression was 1.7 years. Importantly, all patients were confirmed to have the translocation t(17;22).[17,28]

In a separate prospective analysis, 15 patients with metastatic or inoperable DFSP were determined to have the translocation t(17;22) by fluorescent in-situ hybridization.[18,29] Seven patients showed histologic evidence of fibrosarcomatous transformation (FS-DFSP), which can portend more aggressive clinical behavior.[27] Thirteen patients were given IM 800 mg/d and two patients 400 mg/d. 73 percent showed partial response, 7% stable disease, and 20% progressive disease. Five patients with FS-DFSP showed partial response. Interestingly, seven patients underwent surgical resection of residual disease and remained free of disease at follow-up.[29]

McArthur et al[30] also reported a study of 10 patients with DFSP, eight with locally advanced disease, and two with metastatic disease and fibrosarcomatous histology. All were treated with 400 mg IM twice daily. The eight patients with locally advanced disease showed a clinical response, four partial and four complete. Two complete responders underwent follow-up resection, which demonstrated histologic clearance of their tumors. The four partial responders were managed with definitive surgical excision. The two patients

with FS-DFSP, importantly, had a complex karyotype: 1 had evidence of some amount of t(17;22) by fluorescence in situ hybridization and was a partial responder. The other showed no evidence of the COL1A1-PDGFB translocation and died 32 days after therapeutic initiation. An important point to consider from this and the aforementioned studies is the utility of fluorescence in situ hybridization or reverse transcription polymerase chain reaction before treatment to search for the translocation t(17;22), and assess possible response to treatment.

These studies raise other important questions. First, could imatinib be used as neoadjuvant therapy to decrease the size of DFSP before surgical resection, thereby decreasing the morbidity of often-extensive tissue resection? Second, does fibrosarcomatous change in DFSP correlate with lack or loss of t(17;22) expression, or do tumors that lack of t(17;22) represent a sarcoma other than FS-DFSP?

Although the second question awaits further study, Kerob et al[31] addressed the first in a report where 25 patients with primary or recurrent DFSP were treated with IM before surgical resection, with the hope of proving the utility of preoperative therapy. Twenty-one of 25 were shown to harbor the COL1A1-PDGFB fusion gene: two were negative and two were "noninformative." Among the 21 with the fusion gene, 8 (38%) showed partial or complete response after 8 weeks of therapy. The two patients without the gene did not respond. In the responders, the median relative tumoral decrease was 20%, and the authors concluded that neoadjuvant treatment of DFSP was warranted in nonresectable DFSP, or when surgery would be difficult or mutilating.

This conclusion was supported by a case series in which four patients with locally advanced or recurrent DFSP were treated with IM before Mohs (and, in 1 case, Mohs followed by traditional surgical) resection.[32] With doses between 400 and 800 mg daily for a period of three to seven months, an average tumor reduction of 39.5% was achieved. Significantly, one patient with DFSP of the medial ankle was able to avoid a more extensive surgical course that might have resulted in functional damage. The investigators also noted histologic changes in the tumors of patients treated with IM, consisting of a decrease in cellularity and increase in hyalinized collagen. These changes have not been reported elsewhere and will require further investigation, as it is not clear whether the histologic alterations are contiguous in DFSP treated with IM, or if the treatment may result in "skip areas," thereby increasing the risk of a false negative margin evaluation. Of note, all patients remained free of recurrence at follow-up between 1.5 and 4 years. In general, IM is well tolerated, but does have common low-grade side effects, including nausea, fatigue, and edema. Rarely do these side effects limit treatment.[27]

On the Horizon

The use of targeted molecular therapy in other types of cancer has opened up a wide range of possibilities in the treatment of DFSP. Of note, nilotinib (Tasigna; Novartis, Basel, Switzerland) is a TK inhibitor with similar efficacy to IM but is generally better tolerated.[30] The use of nilotinib in DFSP has yet to be studied.

Conclusions

Although targeted molecular therapies have yet to supplant surgical intervention as the standard of care in NMSC, emerging evidence is making them an increasingly attractive option in patients with high surgical morbidity or inoperable tumors. The coming years and further research will help to delineate their place in treatment paradigms.

References

1. Lebwohl M: Actinic keratosis: Epidemiology and progression to squamous cell carcinoma. Br J Dermatol 149:31-33, 2003 (suppl 66)
2. Gold KA, Lee HY, Kim ES: Targeted therapies in squamous cell carcinoma of the head and neck. Cancer 115:922-935, 2009
3. Maubec E, Duvillard P, Velasco V, et al: Immunohistochemical analysis of EGFR and HER-2 in patients with metastatic squamous cell carcinoma of the skin. Anticancer Res 25:1205-1210, 2005
4. Ching S, Low I, Ng D, et al: Epidermal growth factor receptor: a novel biomarker for aggressive head and neck cutaneous squamous cell carcinoma. Human Pathol 39:344-349, 2008
5. Detmar M, Velasco P, Richard L, et al: Expression of vascular endothelial growth factor induces an invasive phenotype in human squamous cell carcinomas. Am J Pathol 156:159-167, 2000
6. Harrington KJ, Kazi R, Bhide SA, et al: Novel therapeutic approaches to squamous cell carcinoma of the head and neck using biologically targeted agents. Indian J Cancer 47:248-259, 2010
7. Sundvall M, Karrila A, Nordberg J, et al: EGFR targeting drugs in the treatment of head and neck squamous cell carcinoma. Expert Opin Emerg Drugs 15:185-201, 2010
8. Goerner M, Seiwert TY, Sudhoff H: Molecular targeted therapies in head and neck cancer—An update of recent developments. Head Neck Oncol 2:8, 2010
9. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567-578, 2006
10. Vermorken JB, Mesia R, Rivera F, et al: Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359:1116-1127, 2008
11. Genmab. Available at: http://www.genmab.com/Science%20And%20Research/Products%20in%20Development/Zalutumumab.aspx. Accessed January 31, 2011
12. Panitumumab. Available at: http://www.cancer.gov/search/resultsclinicaltrials.aspx?protocolsearchid=8073033. Accessed January 31, 2011
13. Kerob D, Dupuy A, Reygagne P, et al: Facial hypertrichosis induced by cetuximab, an anti-EGFR monoclonal antibody. Arch Dermatol 142:1656-1657, 2006
14. Molinari E, De Quatrebarbes J, Andre T, et al: Cetuximab-Induced Acne. Dermatology 211:330-333, 2005
15. Wang LX, Agulnik M: Promising newer molecular-targeted therapies in head and neck cancer. Drugs 68:1609-1619, 2008
16. Gold KA, Lee H-Y, Kim ES: Targeted therapies in squamous cell carcinoma of the head and neck. Cancer 115:922-935, 2009
17. Sorafenib tosylate. Available at: http://www.cancer.gov/search/ResultsClinicalTrials.aspx?protocolsearchid=8115987. Accessed January 31, 2011
18. Degen A, Satzger I, Voelker B, et al: Does basal cell carcinoma belong to the spectrum of sorafenib-induced epithelial skin cancers? Dermatology 221:193-196, 2010
19. Michaelis JP, Henry S, Zanetta S, et al: Phase II study of sunitinib in recurrent or metastatic squamous cell carcinoma of the head and neck: GORTEC 2006-01. J Clin Oncol 28:21-28, 2010
20. Goldberg LH, Firoz BF, Weiss GJ, et al: Basal cell nevus syndrome: A brave new world. Arch Dermatol 146:17-19, 2010

21. Stanton BZ, Peng LF: Small-molecule modulators of the Sonic Hedgehog signaling pathway. Mol Biosyst 6:44-54, 2010
22. Robarge KD, Brunton SA, Castanedo GM, et al: GDC-0449—A potent inhibitor of the hedgehog pathway. Bioorg Med Chem Lett 19:5576-5581, 2009
23. Von Hoff DD, LoRusso PM, Rudin CM, et al: Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. N Engl J Med 361:1164-1172, 2009
24. Yauch RL, Dijkgraaf GJP, Alicke B, et al: Smoothened mutation confers resistance to a hedgehog pathway inhibitor in medulloblastoma. Science 326:572-574, 2009
25. The Purpose of This Study is to Determine The Efficacy and Safety of a Systemic Hedgehog Pathway Antagonist (GDC-0449) in Patients With Basal Cell Nevus Syndrome (BCNS). Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=653206&version=HealthProfessional&protocolsearchid=8120868. Accessed January 31, 2011
26. Peukert S, Miller-Moslin K: Small-molecule inhibitors of the hedgehog signaling pathway as cancer therapeutics. Chemmedchem 5:500-512, 2010
27. McArthur GA: Dermatofibrosarcoma protuberans: Recent clinical progress. Ann Surg Oncol 14:2876-2886, 2007
28. Rutkowski P, Von Glabbeke M, Rankin CJ, et al: Imatinib mesylate in advanced dermatofibrosarcoma protuberans: Pooled analysis of two phase II clinical trials. J Clin Oncol 28:1772-1779, 2010
29. Rutkowski P, Debiec-Rychter M, Nowecki Z, et al: Treatment of advanced dermatofibrosarcoma protuberans with imatinib mesylate with or without surgical resection. J Eur Acad Dermatol Venereol 25:264-270, 2011
30. McArthur GA, Demetri GD, van Oosterom A, et al: Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: Imatinib Target Exploration Consortium Study B2225. J Clin Oncol:23:866-873, 2005
31. Kerob D, Procher R, Verola O, et al: Imatinib mesylate as a preoperative therapy in dermatofibrosarcoma: Results of a multicenter phase II study of 25 patients. Clin Cancer Res 16:3288-3295, 2010
32. Han A, Chen EH, Niedt G, et al: Neoadjuvant imatinib therapy for dermatofibrosarcoma protuberans. Arch Dermatol 145:792-796, 2009