Systemic Medications Linked to an Increased Risk for Skin Malignancy

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Over the last several decades, many new drugs that target molecular pathways in carcinogenesis and the inflammatory immune system have been developed, resulting in substantial improvements in the treatment of many malignancies and inflammatory conditions. However, an increasingly widespread deployment of these new drugs has revealed an increased tendency for patients to develop skin malignancy in some instances and questions of possible association between their use and skin cancer. Specifically, increased skin cancer risk has been reported in association with \textit{BRAF} inhibitors, sonic hedgehog–inhibiting agents, Janus kinase (JAK) inhibitors, and phosphodiesterase 5 (PDE-5) inhibitors. We review the literature and data regarding the significance and strength of these associations and the molecular pathways by which these medications promote cutaneous tumorigenesis. The association of skin cancer with drugs that either induce photosensitivity—nonsteroidal anti-inflammatory drugs, antibiotics (eg, tetracyclines, fluoroquinolones, trimethoprim-sulfamethoxazole), voriconazole, thiazides—or suppress the immune system—certain biologics (eg, anti–tumor necrosis factor agents), calcineurin inhibitors, thiopurines, methotrexate, cyclosporine—is well known and is therefore not reviewed in this discussion.

\textbf{BRAF Inhibitors}

The mitogen-activated protein kinase (MAPK) pathway (also known as the RAS/RAF/MAPK signaling pathway) is important in growth factor–receptor signaling and plays a key role in cell differentiation, survival, and proliferation. Activating mutations in this pathway allow cells to grow and proliferate in a growth factor–independent manner. Twenty percent of human cancers harbor a mutation in the \textit{RAS} oncogene, an upstream mediator of the pathway.\textsuperscript{1} Activating mutations in \textit{BRAF}, a serine/threonine kinase, predominate in cutaneous melanoma and also have been found in 40% to 70% of papillary thyroid malignancies.
10% to 20% of cholangiocarcinomas, and 5% to 20% of colorectal carcinomas. The most common BRAF mutation in cutaneous melanoma is V600E, which involves a glutamic acid for valine substitution at codon 600. This mutation activates BRAF 500-fold and is present in approximately 50% of melanomas.1,2

Vemurafenib, a selective BRAF inhibitor, was approved by the US Food and Drug Administration (FDA) for the treatment of metastatic melanoma in the United States in 2011. Phase 3 trial data demonstrated that vemurafenib resulted in improved survival and decreased risk for disease progression compared to dacarbazine, the former best treatment.3 During phase 1 testing, it became apparent that vemurafenib treatment was associated with a 31% increased risk for squamous cell carcinoma (SCC), most commonly well-differentiated SCC, and keratoacanthomas (KAs).4 This association was confirmed in phase 2 and 3 studies, though the incidence was lower. McArthur et al5 reported a 19% incidence of cutaneous SCC with extended follow-up analysis of the phase 3 trial. Dabrafenib, another BRAF inhibitor, has been similarly associated with increasing the risk for SCC and KA.

In one study, the mean time to development of SCC after initiating vemurafenib therapy was 10 weeks, with lesions reported as early as 3 weeks. Most patients had clinical signs of chronically sun damaged skin; however, a history of SCC was present in only 17%. Most lesions (63%) were characterized as KAs.6

The mechanism for BRAF inhibitor–induced squamous-proliferative growth is due to paradoxical activation of the MAPK pathway in cells with wild-type BRAF that harbor upstream-activating mutations in RAS or tyrosine kinase receptors.7 In the presence of a BRAF inhibitor, inactivated BRAF forms heterodimers with wild-type CRAF (a BRAF-CRAF heterodimer). The heterodimer forms a complex with the mutant RAS that leads to transactivation of the CRAF molecule, resulting in a paradoxical increase in MAPK signaling and consequent ERK phosphorylation and activation through CRAF signaling. RAS, particularly HRAS, mutations have been found in 60% of all vemurafenib-associated SCCs and KAs. For this reason, it is thought that vemurafenib potentiates tumorigenesis in subclinical lesions harboring upstream MAPK pathway mutations as opposed to inducing de novo lesions.8

Because BRAF inhibitors are remarkably efficacious in the treatment of metastatic melanomas harboring the V600E BRAF mutation, there are no restrictions on their use, despite the known increased risk for SCC. Squamous cell carcinomas tend to be low grade, and all tumors that developed in phase 1 to 3 trials were treated with simple excision. The development of SCC did not necessitate interruption of treatment. Furthermore, the addition of MEK inhibition to BRAF inhibitor therapy reduces the risk for SCC from 19% to 7%.7,9,10,11

In addition to SCC, second primary melanomas (SPMs) have been reported in patients treated with BRAF inhibitors. It has been shown that these melanomas occur in melanocytes with wild-type BRAF. It has been postulated that some of these tumors occur in cells that harbor upstream mutations in RAS, whereas others might result from alternate signaling through non-RAF oncogenic pathways.1,12

Zimmer et al1 reported 12 SPMs in 11 patients treated with BRAF inhibitor therapy. They reported a median delay of 8 weeks (range, 4–27 weeks) for SPM development. Tumors were detected in early stages; 1 tumor harbored an NRAS mutation.1

Dalle et al13 reported 25 SPMs in 120 vemurafenib-treated patients. Median delay in SPM development was 14 weeks (range, 4–42 weeks). All tumors were thin, ranging from in situ to 0.45-mm thick. Wild-type BRAF was detected in the 21 melanomas sampled; 1 lesion showed mutated NRAS.13

The exact incidence of SPM in the setting of BRAF inhibition is thought to be at least 10-fold less than SCC and KA.2 Patients on BRAF inhibitor therapy should have routine full-body skin examinations, given the increased risk for SPM and SCC.

Another drug belonging to the tyrosine kinase inhibitor family, sorafenib, is used in the treatment of solid tumors, particularly hepatocellular and renal cell carcinomas, and also has been associated with development of cutaneous SCC and KAs.14 Sorafenib is a multiple tyrosine kinase inhibitor that also inhibits the RAF serine/threonine kinases. Similar to vemurafenib and dabrafenib, SCCs and KAs associated with sorafenib tend to arise in patients with chronic actinic damage during the first 2 months of treatment. It has been hypothesized that inhibition of RAF kinases is pathogenic in inducing SCCs because these lesions have not been reported with sunitinib, another multiple tyrosine kinase inhibitor that lacks the ability to inhibit serine/threonine kinases.15,16 Although SCCs and KAs associated with sorafenib tend to be low grade, it is reasonable to consider sunitinib or an alternative tyrosine kinase inhibitor in patients who develop multiple SCCs while taking sorafenib.16

**Sonic Hedgehog–Inhibiting Agents**

Vismodegib, the first small molecule inhibitor of the signaling protein smoothened, gained FDA approval for the treatment of metastatic or locally advanced basal cell carcinoma (BCC) in 2012. A second agent with an identical mechanism of action, sonidegib, was approved by the FDA for locally advanced BCC in 2015. Approximately 90% of BCCs contain mutations in the sonic hedgehog pathway, which lead to constitutive smoothened activation and uncontrolled cell proliferation.17 The development of smoothened inhibitors introduced a much-needed treatment for inoperable or metastatic BCC, though long-term utility is limited by drug resistance with extended use in this patient population.19,20 Several case reports have documented the emergence of KA22 and cutaneous SCC following vismodegib treatment of advanced
or metastatic BCC. A larger case-control study by Mohan et al showed that patients with BCC treated with vismodegib had an increased risk for non-BCC malignancy (hazard ratio [HR]=6.37), most of which were cutaneous SCC (HR=8.12).

The mechanism by which selective inhibition of smoothened leads to cutaneous SCC is unclear. A study found that patients on vismodegib who developed SCC within the original BCC site had elevated ERK levels within tumor tissue, suggesting that the RAS/RAF/MAPK pathway can become upregulated during hedgehog inhibition. Other studies looking at hedgehog inhibition in medulloblastoma models also have shown activated RAS/RAF/MAPK pathways. These findings suggest that tumors under smoothened inhibition might be able to bypass the sonic hedgehog pathway and continue to grow by upregulating alternative growth pathways, such as RAS/RAF/MAPK.

The incidence of cutaneous SCC following vismodegib treatment is unknown. Chang and Oro examined BCC tumor regrowth from secondary (acquired) resistance to vismodegib and noted that lesions recurred within 1 cm of the original tumor 21% of the time. Although none of the 12 patients whose tumors regrew during treatment were reported to have developed SCC, several demonstrated different BCC subtypes than the pretreatment specimen. The authors proposed that regrowth of BCC was due to upregulated alternative pathways allowing tumors to bypass smoothened inhibition, which is similar to the proposed mechanism for SCC development in vismodegib patients.

Prospective studies are needed to confirm the link between vismodegib and cutaneous SCC. Establish the incidence of SCC development; and identify any pre-treatment factors, tumor characteristics, or treatment details (e.g., dosage, duration) that might contribute to SCC development. Furthermore, because Mohan et al observed that vismodegib-treated patients were less likely to develop SCC in situ than controls, it is unknown if these tumors are more aggressive than traditional SCC. At this point, careful surveillance and regular full-body skin examinations are advised for patients on vismodegib for treatment of advanced BCC.

**JAK Inhibitors**

Another class of medications potentially associated with increased development of nonmelanoma skin cancer (NMSC) is the JAK inhibitors (also known as jakinibs). Many proinflammatory signaling pathways converge on the JAK family of enzymes—JAK1, JAK2, JAK3, and TYK2. These enzymes operate in cytokine signal transduction by phosphorylating activated cytokine receptors, which allows for recruitment and activation by means of phosphorylation of transcription factors collectively known as signal transducers and activators of transcription (STATs). Phosphorylated STATs dimerize and translocate to the nucleus, acting as direct transcription promoters. Janus kinase inhibitors modulate the immune response by reducing the effect of interleukin and interferon signaling.

Ruxolitinib, a JAK1/JAK2 inhibitor, was the first JAK inhibitor approved by the FDA and is indicated for the treatment of myelofibrosis and polycythemia vera. Additionally, oral and topical JAK inhibitors have shown efficacy in the treatment of psoriasis, rheumatoid arthritis, alopecia areata, vitiligo, and pruritus from atopic dermatitis.

The JAK-STAT pathway is complex, and the biological activity of the pathway is both proinflammatory and procell survival and proliferation. Because signaling through the pathway can increase angiogenesis and inhibit apoptosis, inhibition of this pathway has been exploited for the treatment of some tumors. However, inhibition of interferon and proinflammatory interleukin signaling also can potentially promote tumor growth by means of inhibition of downstream cytotoxic T-cell signaling, theoretically increasing the risk for NMSC. A study examining the 5-year efficacy of ruxolitinib in myelofibrosis patients (COMFORT-II trial) found that 17.1% of patients developed NMSC compared to only 2.7% of those on the best available therapy. After adjustment by patient exposure, the NMSC rate was still doubled for ruxolitinib-treated patients compared to controls (6.1/100 patient-years and 3.0/100 patient-years, respectively). Eighty-week follow-up of the phase 3 clinical trial of ruxolitinib for the treatment of polycythemia vera also noted an increased incidence of NMSC, albeit a more conservative increase. Patients randomized to the ruxolitinib treatment group developed NMSC at a rate of 4.4/100 patient-years, whereas the rate for controls treated with best available therapy was 2.7/100 patient-years. In contrast, 5-year follow-up of the COMFORT-I trial, also examining the efficacy of ruxolitinib in myelofibrosis, showed no increased risk for NMSC between ruxolitinib-treated patients and placebo (2.7/100 patient-years and 3.9/100 patient-years, respectively).

A 2017 case series described 5 patients with myelofibrosis who developed multiple skin cancers with aggressive features while receiving ruxolitinib. Duration of ruxolitinib therapy ranged from 4 months to 4 years; 3 patients had a history of hydroxyurea exposure, and only 1 patient had a history of NMSC. High-risk cutaneous SCC, undifferentiated pleomorphic sarcoma, and lentigo maligna melanoma (Breslow thickness, 0.45 mm) were among the tumors reported in this series. Although no definitive conclusion can be made regarding the causality of JAK inhibitors in promoting these tumors, the association warrants further investigation. Clinicians should be aware that ruxolitinib might amplify the risk for NMSC in patients with pre-existing genetic or exposure-related susceptibility. Interruption of drug therapy may be necessary in managing patients who develop an aggressive tumor.

In contrast, tofacitinib, which specifically inhibits JAK3, carries very low risk, if any, for NMSC when used...
for the treatment of psoriasis and rheumatoid arthritis. Results from 2 phase 3 trials analyzing the efficacy of tofacitinib in psoriasis demonstrated that only 2 of 1486 patients treated developed NMSC compared to none in the control group. Furthermore, analysis of NMSC across the tofacitinib rheumatoid arthritis clinical program, which included a total of 15,103 patient-years of exposure, demonstrated that the overall NMSC incidence was 0.55 for every 100 patient-years. Of note, the risk in patients receiving high-dose treatment (10 mg vs 5 mg) was nearly doubled in long-term follow-up studies (0.79/100 patient-years and 0.41/100 patient-years, respectively). Overall, the study concluded that treatment with tofacitinib presents no greater increased risk for NMSC than treatment with tumor necrosis factor inhibitors.

PDE-5 Inhibitors
Phosphodiesterase 5 inhibitors, such as sildenafil citrate, have been widely prescribed for the treatment of erectile dysfunction. Studies have shown that BRAF-activated melanomas, which occur in approximately 50% to 70% of melanomas, also result in reduced PDE-5 expression. In these melanomas, downregulation of PDE-5 results in increased intracellular calcium, which has been shown to induce melanoma invasion. Given this similarity in molecular pathway between BRAF-activated melanomas and PDE-5 inhibitors, there has been increased concern that PDE-5 inhibitors might be associated with an increased risk for melanoma.

In 2014, Li et al published a retrospective analysis suggesting an association with sildenafil and an increased risk for melanoma. Their study utilized the Health Professionals Follow-up Study to identify a statistically significant elevation in the risk for invasive melanoma with both recent sildenafil use (multivariate-adjusted HR=2.24) and use at any time (HR=1.92). These results controlled for confounding variables, such as presence of major chronic disease, use of other erectile dysfunction treatments, family history of melanoma, history of sun exposure, and UV index of the patient’s residence. Notably, the study also found that sildenafil did not affect the incidence of BCC or SCC.

In 2015, Loeb et al also examined the potential association between PDE-5 inhibitors and melanoma. Review of several Swedish drug and cancer registries allowed for analysis of melanoma risk and PDE-5 inhibitor use, based on number of prescriptions filled and type of PDE-5 inhibitor prescribed. Their analysis showed that men developing melanoma were more likely than nonmelanoma controls to have taken a PDE-5 inhibitor (11% vs 8%). In a subgroup analysis, however, statistical significance was shown for men with only a single prescription filled (34% of cases; P<0.05), whereas the difference for men with multiple filled prescriptions did not meet statistical significance. Furthermore, the study did not find increased risk with longer-acting tadalafil and vardenafil (odds ratio [OR]=1.16) compared to sildenafil (OR=1.14). Last, use of PDE-5 inhibitors was only associated with stage 0 (OR=1.49) and stage I (OR=1.21) tumors, not with stages II to IV (OR=0.83) tumors. Although there was a statistically significant association between PDE-5 inhibitors and malignant melanoma (P<0.05), the subgroup analysis findings pointed away from a causal relationship and likely toward a confounding of variable(s).

A 2016 study by Lian et al looked at the risk for melanoma in a cohort of patients diagnosed with erectile dysfunction. No association between PDE-5 inhibitors and melanoma risk was shown when comparing patients who received a PDE-5 inhibitor and those who did not receive a PDE-5 inhibitor. However, secondary analysis did show that melanoma risk was increased among patients receiving more pills (34%) and prescriptions (30%). The authors concluded that there was no association between PDE-5 inhibitor use and overall increased risk for melanoma, and the increased risk associated with a greater number of pills and prescriptions would require further study.

In contrast, a 2017 meta-analysis by Tang et al of 5 studies (3 of which were the aforementioned trials) concluded that use of PDE-5 inhibitors was associated with a small but significantly increased risk for melanoma (OR=1.12) and BCC (OR=1.14) but not SCC. Furthermore, the study found no evidence of dosage-dependent association between PDE-5 inhibitor use and melanoma risk.

Overall, clinical studies have been inconclusive in determining the risk for melanoma in the setting of PDE-5 inhibitor use. Studies showing an increased rate of melanoma within patient cohorts receiving PDE-5 inhibitors are limited; results might be affected by confounding variables. However, given the similarity in mechanism between PDE-5 inhibitors and HRAS-activated melanomas, it is reasonable to continue research into this potential association.

Conclusion
Since the turn of the century, drugs targeting cell-signaling pathways have been developed to treat inflammatory, oncologic, and immune conditions. The role of immunosuppressants in promoting skin cancer is well established and supported by a vast literature base. However, associations are less clear with newer immunomodulatory and antineoplastic medications. Skin cancer has been reported in association with BRAF inhibitors, sonic hedgehog–inhibiting agents, JAK inhibitors, and PDE-5 inhibitors. In the case of JAK and PDE-5 inhibitors, the increased risk for melanoma and NMSC is somewhat inconclusive; risk is more firmly established for BRAF inhibitors and smoothened inhibitors. For the antineoplastic agents reviewed, the therapeutic effect of cancer regression is well documented, and benefits of continued therapy outweigh the increased risk for skin
cancer promotion in nearly all cases. The value of early detection has been well documented for skin malignancy; therefore, increased skin surveillance and prompt management of suspicious lesions should be a priority for physicians treating patients undergoing therapy with these medications.

REFERENCES