Anticancer therapies associated with secondary cutaneous malignancies: A review of the literature

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Recent advancements in anticancer therapy have produced an array of highly specialized therapeutics that prolong disease-free survival, improve tolerability of treatment, and individualize care. With improved treatments and longer survival, treatment-related toxicities are gaining importance. Dermatologic toxicities are common, with therapy-induced secondary cutaneous malignancies of the most frequent and serious for targeted therapies, immunotherapy, and radiotherapy. Often, these eruptive malignant lesions can be treatment limiting and detrimental to quality of life. As such, dermatologists play an important role in multidisciplinary oncologic care teams for surveillance and management of secondary cutaneous malignancies. Proactive dermatologic supervision yields early diagnosis and treatment of secondary cutaneous malignancies, which limits therapy discontinuation and thus optimizes treatment through both therapeutic achievement and overall well-being. (J Am Acad Dermatol 2020;83:1425-33.)

Key words: immunotherapy; oncodermatology; oncology; radiotherapy; secondary cutaneous malignancy; skin cancer; targeted therapy.

In 2018, the World Health Organization reported more than 18 million new cases of cancer worldwide. Over the last few decades, advancement in anticancer therapies has resulted in the introduction of numerous drugs that precisely target specific molecular pathways involved in carcinogenesis. Many new specialized therapeutics, in addition to radiotherapy, which is still widely used, cause a variety of dermatologic adverse events, including therapy-induced secondary cutaneous malignancies (SCMs). SCM, one of the most frequent and serious dermatologic adverse events, can be therapy limiting and detrimental to quality of life.

Owing to an increasing spectrum of dermatologic toxicities and longer life expectancy in cancer patients, dermatologists are increasingly involved in multidisciplinary oncologic care. An important part of the dermatologist's role should be surveillance for and treatment of SCM. Because many of these treatments are used to treat primary skin malignancies, there is a high likelihood that even the general dermatologist will encounter affected patients. In this review, we summarize anticancer therapies associated with an increased risk of SCM. Therapies discussed include targeted therapies, immunotherapy, and radiotherapy, with reference to primary drug use, epidemiology, mechanistic understanding of SCM development, and treatment options (Table I).

BRAF INHIBITORS

Squamoproliferative lesions

B-type rapidly accelerated fibrosarcoma kinase (*BRAF*) is a serine/threonine protein kinase in the Ras-Raf-mitogen activated protein kinase (MAPK) kinase (MEK)-extracellular signal-regulated kinase (ERK) cellular pathway. *BRAF* mutations have been proven to cause constitutive activation of this pathway in melanocytes, with 60% of melanomas harboring *BRAF* mutations, most commonly V600E.[1] Vemurafenib and dabrafenib are oral small-molecule inhibitors targeting such *BRAF* mutations and are approved for use in *BRAF*-positive advanced and metastatic melanoma.[2] Although *BRAF*

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inhibitors have demonstrated meaningfully improved progression-free survival in these patients, cutaneous toxicities are common.[3-5] Moreover, there is a proven association with increased risk of secondary premalignant and malignant lesions, occurring in up to 31% of patients on *BRAF* inhibitor therapy.[6] These secondary epidermal proliferations range from verrucous keratoses to keratoacanthoma (KA) and invasive cutaneous squamous cell carcinoma (cSCC), with suggestion of accelerated transition through this continuum within weeks to months of *BRAF* inhibitor therapy initiation.[7] Less frequent secondary nonmelanoma skin cancers include oral SCC[8] and multiple recurrent basal cell carcinomas (BCCs).[9]

Factors associated with an increased risk of developing *BRAF* inhibitor–induced cSCC include older age, recent treatment initiation, and previous sun damage. In addition, treatment with vemurafenib has a higher risk of causing cSCC compared with dabrafenib.[10] Combination therapy of a *BRAF* inhibitor with a MEK inhibitor decreases the frequency of SCM compared with *RAF* monotherapy alone,[11] with 1 study reporting cSCC rates of 12.5% on monotherapy and 3.0% with combination therapy.[12] Owing to this improved safety, as well as superior therapeutic efficacy, *BRAF* inhibitor monotherapy is now infrequently used, with combination *BRAF* inhibitor/MEK inhibitor therapy predominating.[11,12]

Partial mechanistic understanding of the development of *BRAF* inhibitor–induced cSCCs exists; however, gaps in knowledge remain. One theory is that *BRAF* inhibition induces paradoxic MAPK pathway hyperactivation in *BRAF* wild-type cells with oncogenic *RAS* mutations through increased *RAF* dimerization, which causes constitutive cell proliferation.[6,13,14] However, *RAS* mutations only exist in 60% of associated tumors; thus, alternate pathologic mechanisms must exist.[2] One possibility is the involvement of human papillomavirus and human polyomavirus. Increased viral load of β-subtype human papillomavirus and human polyomavirus may enhance synergism between the effects of these oncogenic viruses, with previous ultraviolet radiation damage in *RAS* wild-type cells facilitating tumorigenesis.[15-19]

CAPSULE SUMMARY

- A variety of anticancer treatments can lead to secondary therapy-induced cutaneous malignancies, which can require treatment discontinuation and disturb quality of life.
- Dermatologists are critical members of oncologic care teams, and patients on specified targeted therapy, immunotherapy, and radiotherapy should undergo surveillance to monitor for and treat secondary cutaneous malignancies.

Given the efficacy of *BRAF* inhibition, therapy may need to be continued despite the potential for a high incidence of SCM. As such, frequent dermatologic evaluation and adequate treatment options are necessary. The mainstay of treatment is surgical excision when possible.[20] Alternate treatments include Mohs micrographic surgery, photodynamic therapy,[20,21] topical[20,22,23] or intralesional[24] 5-fluorouracil, 5-fluorouracil chemowraps,[25,26] and intralesional methotrexate.[27]

Second primary cutaneous melanoma

Squamoproliferative lesions comprise a vast majority of *BRAF* inhibitor–induced SCM. However, development of *BRAF* inhibitor-induced secondary primary melanoma (SPM) has also been described. Although half of cutaneous melanomas carry the *BRAF* V600E-activating mutation, the effect of *BRAF* inhibition on BRAF wild-type melanocytic lesions remains unclear. From early observation, melanoma cells are presumed to exhibit different responses to *BRAF* inhibition according to their *BRAF* status.[28]

Dalle et al[28] commented on these findings in the first report of 5 patients with *BRAF* V600E mutant melanoma on vemurafenib who developed SPM.[28] In response, Chapman et al[29] reported an additional 5 cases among the 464 patients treated with a class I *BRAF* inhibitors in phase II and III clinical trials. Zimmer et al[30] subsequently published a series of 12 SPMs and 9 new dysplastic nevi after selective *BRAF* blockade, and Dalle et al[31] responded to their initial observations with a more thorough investigation, finding 25 more SPMs in this patient population. Lastly, Boussemart et al[14] presented a case series of 31 patients undergoing *BRAF* inhibitor therapy who developed 71 new tumors, 5 of which were SPMs. SPM developed weeks to months after *BRAF* inhibitor initiation, and all but 1 had wild-type *BRAF* status.[32]

Pathogenesis of SPM development remains unknown. Secondary resistance to specific *BRAF* inhibition may be responsible, demonstrating upregulation of phosphorylated ERK activity in the resistant malignant melanocytes.[30] Further pathophysiologic investigation is required; meanwhile, appropriate surveillance strategies must be maintained.

Abbreviations used:

BCC:	basal cell carcinoma
BRAF:	B-type rapidly accelerated fibrosarcoma kinase
cSCC:	cutaneous squamous cell carcinoma
ERK:	extracellular signal-regulated kinase
KA:	keratoacanthoma
MAPK:	mitogen activated protein kinase
MEK:	mitogen activated protein kinase kinase
MKI:	multikinase inhibitors
PD-1:	programmed cell death-1
SCC:	squamous cell carcinoma
SCM:	secondary cutaneous malignancy
SPM:	secondary primary melanoma

MULTIKINASE INHIBITORS

Unlike the specific BRAF inhibitors, sorafenib and sunitinib are multikinase inhibitors (MKIs) that target numerous protein kinases in cell growth and survival pathways. These oral small-molecule MKIs are used in the treatment of solid cancers, most notably metastatic renal cell carcinoma and advanced hepatocellular carcinoma. Dermatologic adverse events are commonly encountered among these.[33] SCMs are more frequent in patients treated with sorafenib, with 1 series estimating the incidence of SCMs at 13.5% in patients on sorafenib vs 6.3% in those on sunitinib.[34] This disparity is attributed to slight differences in molecular targets of the drugs. Although both inhibit multiple tyrosine kinases, sorafenib also targets serine/threonine kinases, and subsequent activation of the MAPK pathway through *BRAF* inhibition may be responsible for sorafenib's increased cutaneous toxicity. This dose-dependent *BRAF* inhibitor–induced cutaneous toxicity substantiates the rates of SCM across the classes of drugs sharing this mechanism.[13]

Since 2006, when Lacouture et al[35] reported the first cases of MKI-induced SCM, multiple publications have described a wide spectrum of squamoproliferative lesions,[36-39] including follicular infundibular ectasia, inflamed actinic keratoses, KAs, and invasive cSCC.[36] An association between MKIs and secondary BCCs has also been suggested, but no adequate mechanisms have been determined. A possible coincident nature leaves this association up to question.[34,40]

Although risk factors are not clearly established, these malignant squamoproliferative lesions tend to manifest on sun-exposed areas, months after MKI initiation, and in patients who had already experienced an MKI-associated cutaneous adverse event.[39,41,42]

Because of the importance of maintaining appropriate treatment of the underlying malignancy, SCMs are not an indication for MKI discontinuation. If present, lesions can be surgically removed with negligible risk of relapse. If surgery is contraindicated, the MKI can be temporarily held with predictable rapid resolution of all lesions.[33] In addition, spontaneous resolution of lesions has been reported when MKI therapy is switched from sorafenib to sunitinib.[39] Systemic retinoids have been suggested for chemoprophylaxis, but sufficient data supporting their efficacy are lacking.[43]

JANUS KINASE INHIBITORS—RUXOLITINIB

Ruxolitinib is a Janus kinase 1 and 2 inhibitor that blocks intracellular nonreceptor tyrosine kinases.[44] Ruxolitinib was originally approved for treatment of hematologic and rheumatologic disease, particularly myelofibrosis and polycythemia vera. Subsequently, Janus kinase inhibitors have also demonstrated efficacy in various dermatologic conditions and are approved for graft versus host disease.[45] As with most immunosuppressive agents, there is a risk of SCM, specifically SCC, and as such, current prescribing information recommends routine full-body skin examination.

There have been 8 cases of ruxolitinib-induced SCM reported to date, all with aggressive biologic behavior.[44-47] In addition, Aboul-Fettouh et al[44] reported 5-year efficacy data on ruxolitinib, which showed that the rate of development of nonmelanoma skin cancers in patients treated with ruxolitinib was 17.1% compared with 2.7% in patients on next best available therapy for myelofibrosis.[44] In the series of 5 cases reported by Blechman et al,[46] all patients developed multiple cSCC as well as 1 patient who additionally developed lentigo maligna melanoma and another who developed metastatic undifferentiated pleomorphic sarcoma. Despite aggressive surgical treatment, many of these SCMs recurred, which is suggested to be due to early perineural invasion.[45] As such, magnetic resonance imaging may be indicated in patients on ruxolitinib with cutaneous malignancies to assess for the presence of this invasion and plan for wide local excision accordingly.[45]

Because long-term data are not yet available, the true characteristics of Janus kinase inhibitor–associated SCM cannot be well classified. However, it remains crucial to closely monitor all patients on ruxolitinib during and after treatment to facilitate early diagnosis and management of potentially aggressive skin cancers.

SONIC HEDGEHOG INHIBITORS—VISMODEGIB

BCC is the most common malignancy in the United States. Surgical resection is not effective for

Table I. Overview of anticancer therapies associated with secondary cutaneous malignancies (*SCM*)

Drug class	Generic drug names	Approved indications	Associated SCM	Risk factors for SCM development	Treatment options	Other cutaneous toxicities
BRAF inhibitors	Vemurafenib, dabrafenib	-Advanced and metastatic melanoma -Nonsmall cell lung cancer -Papillary thyroid cancer -Colorectal cancer -Renal cell carcinoma	-Squamoproliferative lesions: verrucous keratoses, keratoacanthoma (KA), squamous cell carcinoma (SCC) -Second primary melanoma (SPM)	Older age, recent treatment initiation, previous UV damage, treatment with vemurafenib Speculated- longer duration of BRAFi use → BRAFi resistance → SPM	First line—surgical excision Second line—Mohs micrographic surgery, photodynamic therapy, topical 5-fluorouracil, intralesional methotrexate Surgical excision	Generalized rash, palmoplantar erythrodysthesia, pruritus, alopecia, photosensitivity
Multikinase inhibitors	Sorafenib, sunitinib	-Metastatic renal cell carcinoma -Advanced hepatocellular carcinoma	-Squamoproliferative lesions- follicular infundibular ectasia, cystic folliculitis, inflamed actinic keratoses, KA, SCC -Basal cell carcinoma (BCC)	Previous UV damage, recent treatment initiation	First line—surgical excision Second line—MKI substitution of sunitinib for sorafenib, MKI discontinuation Chemoprophylaxis-systemic retinoids	Palmoplantar erythrodysthesia, erythema, xerosis, pruritus, alopecia
Janus kinase inhibitors	Ruxolitinib	-Myelofibrosis -Polycythemia vera	SCC	Unknown	MRI imaging to assess for perineural invasion → if yes, wide local excision, if no standard surgical excision	Rash, herpes zoster
Sonic hedgehog inhibitors	Vismodegib	-Locally advanced or metastatic BCC -Basal cell nevus syndrome	SCC	Speculated- previous UV damage, metatypical BCC	Surgical excision	Alopecia, folliculitis, dermal hypersensitivity
Programmed cell death-1 inhibitors	Pembrolizumab, nivolumab, cemiplimab	-Metastatic melanoma -Non-small cell lung cancer -Head and neck squamous cell carcinoma -Metastatic cutaneous squamous cell carcinoma	KA, invasive cSCC, BCC	Unknown	Treatment—topical and intralesional steroids with or without superficial cryotherapy Chemoprophylaxis—systemic retinoids	Maculopapular rash, pruritus, urticarial dermatitis, lichenoid reactions, vitiligo, cutaneous sarcoidosis, bullous pemphigoid, psoriasis

Radiotherapy	-Benign and malignant tumors	BCC	Radiation-dependent: higher total dose or irradiation, modality of RT, time since RT, increased UV susceptibility, younger age at time of irradiation Radiation-independent: genetic predisposition, alcohol, tobacco, and exposure to other carcinogens	Mechanical, chemical, or thermal destruction	Radiation dermatitis (pruritus, hyperpigmentation, erythema, edema, blistering, dry/wet desquamation, necrosis)

BRAF(i), B-type rapidly accelerated fibrosarcoma kinase (inhibitor); *cSCC*, cutaneous squamous cell carcinoma; *MKI*, multikinase inhibitors; *MRI*, magnetic resonance imaging; *RT*, radiotherapy; *UV*, ultraviolet.

locally advanced or metastatic disease, and when radiotherapy is contraindicated, treatment options are limited.[48] In 2012, vismodegib was approved for use in these patients as well as in those with basal cell nevus syndrome. Vismodegib is a small-molecule inhibitor of *Smoothened* (*SMO*), which is a key component of the hedgehog signaling pathway. Approximately 90% of sporadic BCCs have a mutation in *SMO* or *Patch*, a closely linked upstream gene in the hedgehog pathway. These mutations induce constitutive activation of cell proliferation, which drives tumorigenesis.[49] Immediate efficacy of vismodegib for treatment of BCC is established; however, long-term effects have yet to be reported.

Vismodegib has been speculated to increase the risk for development of SCM, with 7 cases reported in the literature[49-52] as well as 1 case-control study demonstrating this association.[53] Most affected patients had no history of cSCC and developed new eruptive biopsy specimen-proven SCC within weeks to months of therapy initiation. Several hypotheses for the mechanism of vismodegib-induced cSCC have been suggested.

Iarrobino et al[51] suggested that vismodegib causes selection for a subpopulation of SCC cells already present or that alteration in the hedgehog pathway results in squamous differentiation of existing malignant basal cells.[51] Saintes et al[49] speculated that vismodegib therapy may result in residual squamous contingent in metatypical BCC and proposed that repeat biopsy of areas on nonresolving lesions is essential to detect these squamous proliferations for which local excision is necessary.[49]

Lastly, Mohan et al[53] hypothesized that *SMO* inhibition activates the *RAS*/MAPK pathway, which eliminates dependency on the hedgehog pathway for tumorigenesis. Subsequently, surrounding epidermal cells with malignant potential due to high mutational loads from previous ultraviolet damage undergo malignant transformation, with hedgehog inhibition as the tipping point.[53]

Owing to the observational nature of these reports, causality cannot be substantiated. In addition, coincidental field cancerization by ultraviolet radiation or radiotherapy is difficult to quantify. Nonetheless, the time course of cSCC development within weeks after vismodegib initiation suggests this association may exist and that close dermatologic monitoring during vismodegib therapy is prudent. Of note, SCM have never been described in patients treated with sonidegib, another agent in this class approved in 2015 for use in locally advanced BCC[54]; however, close surveillance in patients receiving this therapy remains sensible.

PROGRAMMED CELL DEATH-1 INHIBITORS

Programmed cell death-1 (*PD-1*) inhibitors (eg, pembrolizumab, nivolumab, and cemiplimab) are immunomodulatory agents that uniquely hone and unleash the host immune system as an antitumor combatant. These fastidious pharmacologic agents are used in the treatment of a variety of solid tumors, including metastatic melanoma and metastatic cSCC.[55] While robust cytotoxic T-cell activation facilitates antitumor activity, it is also responsible for a multitude of immune-related adverse events.[56,57] Late-phase clinical trial data reveals an incidence of 15% to 41% for immune-related adverse events with immunomodulatory monotherapy, whereas risk increases to 60% with combination immunotherapy.[58]

Paradoxically, while *PD-1* inhibitors have been successfully used to treat cSCC, there have been 5 reported cases of therapy-induced squamoproliferative lesions, including eruptive KA[55] and invasive cSCC[57,59] as well as 1 BCC. In the cases of eruptive KA, dermal infiltrate resembled the immunophenotypic pattern of *PD-1* inhibitor—induced lichenoid dermatitis, and thus, an immune-mediated mechanism was proposed.[55] Interestingly, there are reports of *PD-1* inhibitor-induced invasive cSCC in the setting of concurrent Toll-like receptor 9 agonist therapy as well as combination therapy with pembrolizumab and imiquimod. Authors hypothesized that enhanced Toll-like receptor expression on tumor cells altered the microenvironment to facilitate proliferation of malignant cells.[57,59] *PD-1* inhibitor—induced eruptive KAs were successfully treated with intralesional and topical steroids, with or without superficial cryotherapy, and therapy was continued without disruption.[55] Toll-like receptor 9 agonist therapy was always discontinued if present, and temporary interruption of *PD-1* inhibitor therapy was needed in 1 case.[57,59]

Continued reporting of immunomodulatory agent—induced SCM will be essential in further understanding level of risk, pathophysiology of lesion development, and appropriate management.

RADIOTHERAPY

Although chemotherapeutic agents, such as those previously discussed, play a significant role in the treatment of malignancy, another central facet of anticancer treatment is radiotherapy. Increased survival of cancer patients has made long-term risks of radiotherapy more important, specifically radiotherapy-induced secondary malignancies.[60] Seven years after the introduction of x-rays, the first RT-induced malignancy was reported, which was an SCC on the hand of a radiation worker. Since then, large cohorts of irradiated patients from therapeutic, occupational, and environmental exposures have formed a robust foundation of epidemiologic data for radiotherapy-induced malignancies.[61]

Radiotherapy-induced malignancies are defined as those that develop at the site of irradiation, with a latency period of at least 2 years after initiation of radiotherapy and with distinct histology from the primary tumor.[62,63] Remarkably, a large cancer registry reported in 2011 that 18% of all cancer diagnoses in the United States are secondary malignancies, with 44% of these due to radiotherapy.[64] Further, a large childhood survivorship study reported a secondary malignancy rate of 20.5% at 30 years after the initial diagnosis of a primary malignancy.[65] Radiation is most strongly associated with the development of BCC in a dose-dependent manner. In addition, cutaneous angiosarcoma accounts for 12% of radiotherapy-induced malignancies and is most common after irradiation for breast or gynecologic cancer.[66]

An oncogenic role of c-*MYC* amplification has been implicated in radiation-induced angiosarcoma, without evidence in sporadic tumors. This specific molecular finding is especially unique because it is one of the few known molecular indicators of treatment-associated cancers.[67,68] Case reports and series detail a wide array of additional postradiotherapy skin and soft tissue malignancies, including fibrosarcoma,[69-72] mixed mesenchymal sarcoma,[73] liposarcoma,[74] malignant fibrous histiocytoma,[75,76] and neurogenic sarcoma.[77] These malignancies can occur decades after irradiation, and all share poor prognoses.[78]

Both radiation-dependent and -independent risk factors for the development of radiotherapy-induced SCM exist. Radiation-dependent risk factors include higher total dose of irradiation, modality of radiotherapy (2-dimensional conformal radiotherapy > intensity-modulated radiotherapy > 3-dimensional conformal radiotherapy > proton therapy), increased time elapsed since radiotherapy, increased ultraviolet susceptibility/lighter skin type, and younger age at time of radiation exposure.[60,79,80] Radiation-independent risk factors include genetic predisposition to malignancy, lifestyle aspects (alcohol, tobacco, and medications), and exposure to other carcinogens.[80]

Unfortunately, radiotherapy-induced BCCs tend to be more aggressive, harder to eradicate, and more prone to recurrence than sporadic lesions.[61] As such, patients who have received radiotherapy require close lifetime surveillance by a dermatologist. Remarkably, referral rates to dermatology by

radiation oncologists for surveillance and care of RT-induced skin toxicities and skin cancer screening is low, with a nationwide average of 14.7%.[81] Treatment for radiation-induced BCCs is similar to de novo lesions, including mechanical, chemical, and thermal destruction or surgery.

CONCLUSION

Recent advancements in anticancer therapy have radicalized therapeutic capabilities and individualization of care. With improved treatments and longer survival, treatment-related toxicities, many of which are cutaneous, are gaining importance. As such, dermatologists play a critical role in surveillance and management of oncology patients. As implementation of the discussed anticancer therapeutics increases, a more comprehensive understanding of long-term dermatologic effects will be established. In the interim, routine cutaneous surveillance of patients on systemic anticancer therapies is critical to minimize toxicity-provoked therapy discontinuation, facilitate early diagnosis of skin cancer, better describe the spectrum of anticancer therapy-related adverse events, and improve quality of life.

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