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Pigmentary changes in patients treated with targeted anticancer agents: a systematic review and meta-analysis

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Abstract

Background—The discovery of signaling networks that drive oncogenic processes has led to the development of targeted anticancer agents. The burden of pigmentary adverse events from these drugs is unknown.

Objective—To conduct a systematic review and meta-analysis of published clinical trials, and determine the incidence and risk of developing targeted therapy-induced pigmentary changes.

Methods—A comprehensive search was conducted to identify studies reporting targeted therapy-induced pigmentary changes. The incidence and relative risk were calculated. Case reports and series were reviewed to understand clinical characteristics.

Results—8,052 patients from 36 clinical trials were included. The calculated overall incidences of targeted cancer therapy-induced all-grade pigmentary changes in the skin and hair were 17.7% (95% CI, 11.9–25.4) and 21.5% (95% CI, 14.9–30.1), respectively. The relative risk of all-grade

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pigmentary changes of skin and hair were 93.7 (95% CI: 5.86–1497.164) and 20.1 (95% CI: 8.35–48.248). Across 54 case reports/series (n=75 patients), EGFR and Bcr-abl inhibitors were the most common offending agents.

Limitations—Potential underreporting and variability in oncologists reporting these events.

Conclusion—There is a significant risk of developing pigmentary changes during treatment with targeted anticancer therapies. Appropriate counseling and management are critical to minimize psychosocial impairment and deterioration in quality of life.

Keywords

Cabozantinib; Imatinib; Ipilimumab; Nivolumab; Pazopanib; Pembrolizumab; Sorafenib; Sunitinib; Pigmentary; Hypopigmentation; Hyperpigmentation; Depigmentation; Repigmentation; Dyspigmentation; Vitiligo

INTRODUCTION

The discovery of intracellular signaling networks that drive oncogenic processes when aberrantly activated has led to the development of molecularly targeted agents for the treatment of various cancers [1, 2]. Their targeted action spares normal cells, thus improving efficacy and health-related quality of life (HRQoL). While systemic adverse events (AEs) characteristic of conventional cytotoxic agents (e.g. myelosuppression, nausea, vomiting) [3] are typically not encountered, dermatologic AEs (affecting the skin, hair, nails, mucosae) are common because some of the signaling pathways inhibited are also essential for cutaneous homeostasis [4]. Skin eruptions (rashes), xerosis, pruritus, photosensitivity, pigmentary changes, fissures, hand-foot skin reaction, and hair/nail changes are some of the most commonly encountered targeted therapy-induced dermatologic AEs [5]. Although not life-threatening, they can negatively impact patients' HRQoL, and impair psychosocial functioning and activities of daily living (ADL) [6, 7]. Furthermore, they often result in dose reductions, interruptions, or even discontinuation of therapy, which may lead to suboptimal management of the cancer itself and result in poorer outcomes [8].

Whereas the incidence and risk of some of the targeted therapy-induced dermatologic AEs have been previously estimated [9, 10], that of dermatologic pigmentary AEs (dpAEs) is not known. The latter are of particular concern because of their persistence, resistance to therapy, and negative impact on psychosocial well-being and HRQoL. Therefore, we conducted a systematic review and meta-analysis of the literature to determine the incidence and risk of targeted therapy-induced dermatologic pigmentary AEs.

METHODS

Data source

We searched all targeted anticancer agents (n=64, Appendix I) approved by the Food and Drug Administration (www.FDA.gov) in January 2017. A PubMed search was conducted using the generic name of targeted agents (e.g. "afatinib") as the keyword. The search was limited to phase II and phase III randomized and non-randomized clinical trials (RCT, NRCT) published in English (January 1998 through January 2017). We also reviewed

abstracts and virtual meeting presentations (January 2004 through January 2017) posted on the American Society of Clinical Oncology (ASCO) website to further identify relevant clinical trials. In addition, an independent search on the Web of Science database was also conducted to ensure that no other studies were missed. We reviewed each publication and retrieved data only from complete and/or the most recent reports if duplicate publications were identified. Extracted information included patient characteristics, study design, treatment regimen, study results, and safety data.

Study selection

The U.S. Food and Drug Administration (USFDA) approves targeted therapies at a specific dose in the treatment of cancer. Therefore, we excluded clinical trials employing drugs at unapproved doses (e.g. phase I studies) in order to determine the incidence and risk of dpAEs at the dosing level meaningful for clinicians. We also excluded trials that combined targeted agents with other chemotherapeutic agents and/or treatment modalities. The dpAEs in the studies were reported as: “hyperpigmentation,” “hypopigmentation,” “depigmentation,” “repigmentation,” “dyspigmentation,” “discoloration,” “color change,” and “vitiligo” of either the skin/ hair/ nails. Studies that met the following criteria were selected for final analysis: (1) prospective phase II and III clinical trials in patients with cancer; (2) assignment of participants to treatment with the targeted agent at the approved dose; and (3) availability of data regarding the incidence of pigmentary changes.

Clinical end points

The clinical endpoints were extracted from the safety profile in each trial. The dpAEs for skin were recorded according to the National Cancer Institute’s Common Toxicity Criteria (CTCv2.0), or the Common Terminology Criteria for AEs (CTCAE v3.0 and v4.0). The grading of dpAEs in the skin in version 2.0 is described as follows: grade 0, none; grade 1, localized; grade 2, generalized. In version 3.0, the description was updated to hyperpigmentation and hypopigmentation, as follows: grade 1, slight or localized; grade 2, marked or generalized. Version 4.0 further stratifies hyperpigmentation and hypopigmentation by body surface area (BSA) involvement as follows: grade 1, covering <10% BSA—no psychosocial impact; grade 2, covering >10% BSA—associated psychosocial impact. However, none of the studies in our meta-analysis utilized CTCAE v4.0. Lastly, given that pigmentary changes are not considered life threatening, there is no high-grade designation for these AEs.

Statistical analysis

All statistical analysis was performed using Comprehensive Meta-Analysis program (v2.0, Biostat, Englewood, NJ). The number of patients with pigmentary AEs in treatment and control groups (as applicable) was identified from the selected clinical trials. The incidence and 95% confidence intervals (CIs) were calculated for each trial. For studies with a control arm, the relative risk (RR) of pigmentary AEs was also calculated.

For meta-analysis, both the fixed-effects (weighted with inverse variance) and the random-effects model were given consideration for meta-analysis. The Cochran Q statistic was calculated for each meta-analysis to determine the heterogeneity of the included trials. For *P*

value of Cochran Q statistic less than 0.1, the assumption of homogeneity was deemed invalid, and the random-effects model was employed after exploring the cause of heterogeneity. Barring this phenomenon, both the fixed-effects and random-effects models were reported. A two-tailed *P* value of less than 0.05 was established as statistically significant.

Systematic review of published case reports and case series

We also reviewed case reports and series to understand the clinical characteristics of dpAEs, as they are not reported in clinical trial publications. For this portion of the study, the following PubMed search strategy was used (last performed in January 2017): generic drug name AND (albinism OR bronz* OR dark* OR darkening OR depigmentation OR discoloration OR dyschromia OR excessive pigmentation OR hyperpigmentation OR hypopigmentation OR light* OR lightening OR melanosis OR poliosis OR repigmentation OR vitiligo OR whit*). The results were narrowed down to case reports and case series published in English. In addition, a manual search of the bibliography from retrieved reports was also performed. One of the authors (JD) reviewed all the identified manuscripts and extracted the following data onto an excel spreadsheet: age, gender, race, underlying cancer, clinical findings, types of dyspigmentation including sites of involvement, pathology findings (if available), drug (including dosing), dose alterations, outcomes, number of cases, first author, year of publication.

RESULTS

Search results

Our literature search yielded a total of 7,604 potentially relevant studies, of which 36 clinical trials that involved targeted anticancer therapies met the inclusion criteria, and were included in the final analysis (Fig 1). The latter included phase II [11–34] (n=24) and phase III [35–46] (n=12) trials—all investigating solid organ malignancies. In all, 8,052 patients (controls, n=3,648; drug, n=4,404) were analyzed across trials employing cabozantinib, imatinib, ipilimumab, nivolumab, pazopanib, pembrolizumab, sorafenib, or sunitinib, which represented 8 major drugs of the 64 (12.5%) included in the search. The data was analyzed separately for dpAEs of the skin and hair.

Incidence of all-grade pigmentary changes in skin

Data for all-grade dpAEs of skin was available for 6,538 patients (across 28 clinical trials) treated with a targeted agent. The calculated overall incidence across all studies was 17.7% (95% CI, 11.9–25.4) according to the random-effects model (heterogeneity test: Q = 416.4, I_2 = 93.5, P <0.001) (Fig 2A). The lowest incidence, 0.7%, was noted in the pazopanib arm (n=554) of a randomized, open-label, phase III trial involving metastatic renal-cell carcinoma patients [39]. The highest incidence, 75%, was noted in a phase II study of sunitinib (n=24) in patients with relapsed or refractory small cell lung cancer [17]. The drug-wise summary incidences of all-grade pigmentary changes are provided in Table 1.

Incidence of all-grade pigmentary changes in hair

In all, we identified 14 clinical trials (involving 3,319 evaluable patients) that reported hair color changes as a result of treatment with a targeted agent. The calculated overall incidence was 21.5% (95% CI, 14.9–30.1) according to the random-effects model (heterogeneity test: Q=191.3, I_2=93.2, P<0.001) (Fig 2B). The lowest incidence, 3.7%, was noted in the sunitinib arm (n=375) of a randomized, double-blinded, phase III trial involving metastatic renal-cell carcinoma patients [41]; in an open-label extension study to evaluate the safety and efficacy of pazopanib in patients with advanced renal-cell carcinoma (n=80), the incidence of hair color changes was highest at 43.8% [43].

Relative risk of all-grade pigmentary changes in skin

In order to estimate the relative risk (RR) of these changes in patients receiving targeted therapies as compared to placebo, a pooled meta-analysis was performed by using RCTs as the control arm. All-grade skin pigmentary changes were noted in 428/3301 patients receiving targeted therapies [11–31, 35–41], as opposed to none (0/360) among patients who received best supportive care (BSC) alone [41]. The calculated overall RR for all-grade changes was 93.7 (95% CI: 5.86–1497.164; P <0.001), according to the random-effects model. The calculated high-grade RR was 2.371 (95% CI: 0.134–42.003; P=0.556).

Relative risk of all-grade pigmentary changes in hair

A meta-analysis of RR for all-grade hair color changes associated with targeted agents versus controls was performed on 3 RCTs [42,44,46]. All-grade hair color changes were noted in 187/536 patients receiving targeted therapies, as compared to 5/314 patients who received BSC alone. The calculated RR was 20.1 (95% CI: 8.35–48.248; P <0.001), according to the fixed-effects model. The calculated high-grade RR was 2.134 (95% CI: 0.224–20.355; P=0.510).

Case reports and Case series

Our search strategy yielded 54 publications (2002–2017) reporting on targeted anticancer therapy-induced dpAEs involving the skin, hair, nails, and mucosae: 45 were case reports (n=45 patients) and 9 were case series (n=30 patients), with single-case reporting representing the majority (45/54 patients, 83%). Given the case-level nature of the reports, we conducted a pooled analysis, and provided a summary of our findings (Table 2)—the raw data pertaining to all cases, their description, and references are provided in Appendix II. The mean patient age was 49.8 years (range: 8 years to 83 years), with a slight preponderance of females (41/75, 54.7%). The time to onset ranged from “immediately” to up to 10 years after initiation of treatment, and most reports (n=30/54, 55.6%) pertained to imatinib (43/75 patients, 57.3%). Accordingly, nearly half of the cases (n=33/75, 44.0%) had been treated for chronic myeloid leukemia (CML). Importantly, only 6/75 cases (8.0%) experienced dose alterations due to dpAEs.

The skin appeared to be the most commonly affected site, followed by involvement of the mucosa, hair, and nails. While generalized skin involvement did occur (n=10), localized affliction of the face (n=36), trunk (n=10), hands/feet (n=8) and legs (n=8), and arms (n=7) was also seen; no specific patterns were identifiable. The outcome of skin dpAEs was noted

in 11/50 (22.0%) cases; resolution in 7/50, 14.0%, and persistence in 4/50, 8.0% cases. The information pertaining to reversibility was not described in the rest. The Bcr-abl inhibitor, imatinib, was responsible for the majority of skin-related dpAEs in this pooled analysis of cases. In cases where hair was affected, scalp hair involvement predominated (10/13, 76.9%), although virtually all hair-bearing areas appear susceptible; inhibitors of the Bcr-abl and VEGFR were the most common culprits. Nail dpAEs included hyperpigmentation and yellow discoloration in a total of 5 cases. Mucosal dpAEs were exclusively seen with imatinib (n=17) and described as a blue-gray to brown discoloration.

DISCUSSION

In this study, we determined the incidence and risk of targeted anticancer therapy-induced dpAEs from the safety data of published clinical trials and attempted to analyze the clinical characteristics by reviewing pertinent case reports/series. We found that the overall incidence of dpAEs in patients exposed to targeted anticancer therapies is high—skin, 17.7% and hair, 21.5%. The targeted agents imatinib, cabozantinib, nivolumab, pazopanib, pembrolizumab, sorafenib, and sunitinib appeared to be the most common culprits.

The pathophysiology of targeted anticancer therapy-induced dpAEs appears to be multifactorial, and remains poorly understood [47]. Pigmentary changes associated with imatinib, a tyrosine kinase inhibitor, are well documented in the literature, with the most commonly described clinical phenotype being reversible, dose-related hypopigmentation [48, 49]. *In vitro* studies demonstrate that imatinib may decrease skin pigmentation by inhibiting tyrosinase activity, likely through blockade of the c-KIT pathway and PDGF inhibition [50]. Interestingly, paradoxical cases of imatinib-associated hyperpigmentation have also been described [51–53], although the mechanisms underlying these differential reactions remain unclear.

Similarly, dpAEs associated with multikinase (MKI) inhibitors are likely due to inhibition of c-KIT, a known regulator of melanogenesis. c-KIT is uniquely expressed in melanocytes and plays a critical role in melanocyte development, differentiation, and maintenance [54]. Mutations in c-KIT are associated with hypopigmentation syndromes such as piebaldism and vitiligo [55, 56]. The non-selective MKIs, cabozantinib, pazopanib, sorafenib, and sunitinib are probably associated with c-KIT inhibition, though perhaps not through a direct effect on the KIT receptor, as with imatinib.

In the case of ipilimumab, however, the pigmentary changes appear to be a direct result of CTLA-4 inhibition and consequent immune system activation, [57] including against the melanocytes [58]. Surprisingly, clinical depigmentation may serve as a surrogate marker for responsiveness to anticancer treatment, with the appearance of vitiligo-like melanoma-associated hypopigmentation portending a favorable response to therapy [59]. Finally, vitiligo-like lesions that occur during treatment with selective PD-1 inhibitors, such as pembrolizumab and nivolumab, have been reported in up to 25% of patients and may be associated with a clinical benefit [60]. A recent study suggests a unique clinical phenotype and pathophysiological pathway that implicates a CD8 T-cell immune response distinct from spontaneously occurring vitiligo [61].

Current management strategies focus on pre-emptive approaches and patient education rather than symptom management, because termination of drug exposure typically leads to resolution of the dpAEs. Patients should also be advised to use appropriate UV protection, as individuals who experience hypopigmentation may be at an increased risk for photosensitivity disorders. Our meta-analysis has several limitations. First, dpAEs are asymptomatic and patients are less likely to notice and/or report them. Second, the assessment and reporting of dpAEs may be variable across healthcare providers and institutions, which could have impacted safety reporting in clinical trials. Therefore, these inconsistencies may have resulted in the underreporting, and consequently, an underestimation of the incidence of targeted anticancer therapy-induced dpAEs.

The study of AEs, especially dermatologic, is yet to keep up with the pace at which newer targeted anticancer drugs are being approved. Herein, we have shown that dpAEs are being encountered by a significant number of cancer patients. This phenomenon is of particular importance because these events bear the potential to negatively impact patients' quality of life and psychosocial well-being, in addition to being long-lasting and challenging to treat. Moreover, the use of these drugs is widening, suggesting that these AEs could be increasingly encountered. Therefore, there is an urgent need to educate patients and healthcare providers and develop effective management strategies. Further investigation into the pathophysiology and management of dpAEs is warranted to ensure optimal therapy and improve patients' quality of life. By understanding the pathogenesis and clinical manifestations of these AEs, dermatologists play a critical role in guiding oncologic therapy by minimizing unwarranted dose reduction and dose stoppage.

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ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ASCO	American Society of Clinical Oncology
Bcr-abl	breakpoint cluster region-abelson
BRAF	B-rapidly accelerated fibrosarcoma proto-oncogene serine–threonine-protein kinase
BSA	body surface area
BSC	best supportive care
CI	confidence interval
CML	chronic myeloid leukemia

CSF	colony-stimulating factor
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen-4
dpAE	dermatologic pigmentary adverse events
EGFR/ EGFRI	epidermal growth factor receptor/ EGFR inhibitor
Flt	fms-like tyrosine kinase
HRQoL	health-related quality of life
Kit	KIT protein
mAb	monoclonal antibody
MEK	MAPK/ERK (Extracellular signal-Regulated Kinase) Kinase
MET	mesenchymal-epithelial transition factor
MKIs	multikinase inhibitor(s)
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	mammalian target of rapamycin
NRCT	non-randomized controlled trial
PDGF/ PDGFR	platelet derived growth factor/ PDGF receptor
Ras	rat sarcoma
Ret	rearranged during transfection
RR	relative risk
RCT	randomized controlled trial
TEK	Tyrosine kinase, endothelial
TIE	Tyrosine kinase with immunoglobulin-like and EGF-like domains
TKI	tyrosine kinase inhibitor
TRKB	tropomyosin receptor kinase B
USFDA	United States Food and Drug Administration
VEGF/ VEGFR	vascular endothelial growth factor/ VEGF receptor

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APPENDIX

Appendix I. List of all targeted agents searched to identify studies reporting dermatologic pigmentary adverse events (n=64)

Ado-trastuzumab emtansine (Kadcyla)

Afatinib dimaleate (Gilotrif)

Alectinib (Alecensa)

Alemtuzumab (Campath)

Atezolizumab (Tecentriq)

Axitinib (Inlyta)

Belinostat (Beleodaq)

Bevacizumab (Avastin)

Blinatumomab (Blincyto)

Bortezomib (Velcade)

Bosutinib (Bosulif)

Brentuximab vedotin (Adcetris)

Cabozantinib (Cometriq)

Carfilzomib (Kyprolis)

Ceritinib (Zykadia)

Cetuximab (Erbitux)

Cobimetinib (Cotellic)

Crizotinib (Xalkori)

Dabrafenib (Tafinlar)

Daratumumab (Darzalex)

Dasatinib (Sprycel)

Dinutuximab (Unituxin)

Elotuzumab (Empliciti)

Erlotinib hydrochloride (Tarceva)

Everolimus (Afinitor)

Gefitinib (Iressa)

Ibrutinib (Imbruvica)

Idelalisib (Zydelig)

Imatinib mesylate (Gleevec)

Ipilimumab (Yervoy)

Ixazomib (Ninlaro)

Lapatinib ditosylate (Tykerb)

Lenvatinib (Lenvima)

Necitumumab (Portrazza)

Nilotinib (Tasigna)

Nivolumab (Opdivo)

Obinutuzumab (Gazyva)

Ofatumumab (Arzerra)

Olaparib (Lynparza)

Olaratumab (Lartruvo)

Osimertinib (Tagrisso)

Palbociclib (Ibrance)

Panitumumab (Vectibix)

Panobinostat (Farydak)

Pazopanib hydrochloride (Votrient)

Pembrolizumab (Keytruda)

Pertuzumab (Perjeta)

Ponatinib (Iclusig)

Ramucirumab (Cyramza)

Regorafenib (Stivarga)

Rituximab (Rituxan)

Romidepsin (Istodax)

Ruxolitinib (Jakafi)

Sorafenib tosylate (Nexavar)

Sonidegib (Odomzo)

Sunitinib malate (Sutent)

Temsirolimus (Torisel)

Trametinib (Mekinist)

Trastuzumab (Herceptin)

Vandetanib (Caprelsa)

Vemurafenib (Zelboraf)

Vismodegib (Erivedge)

Vorinostat (Zolinza)

Ziv-aflibercept (Zaltrap)

Appendix II. Published case reports/series of pigmentary changes during treatment with targeted anticancer agents (n=54)

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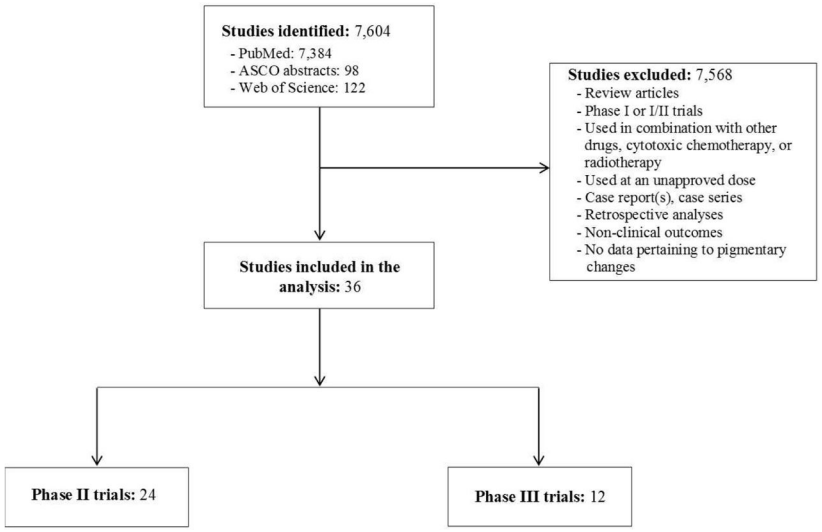

Figure 1.
Selection process for studies included in meta-analysis.

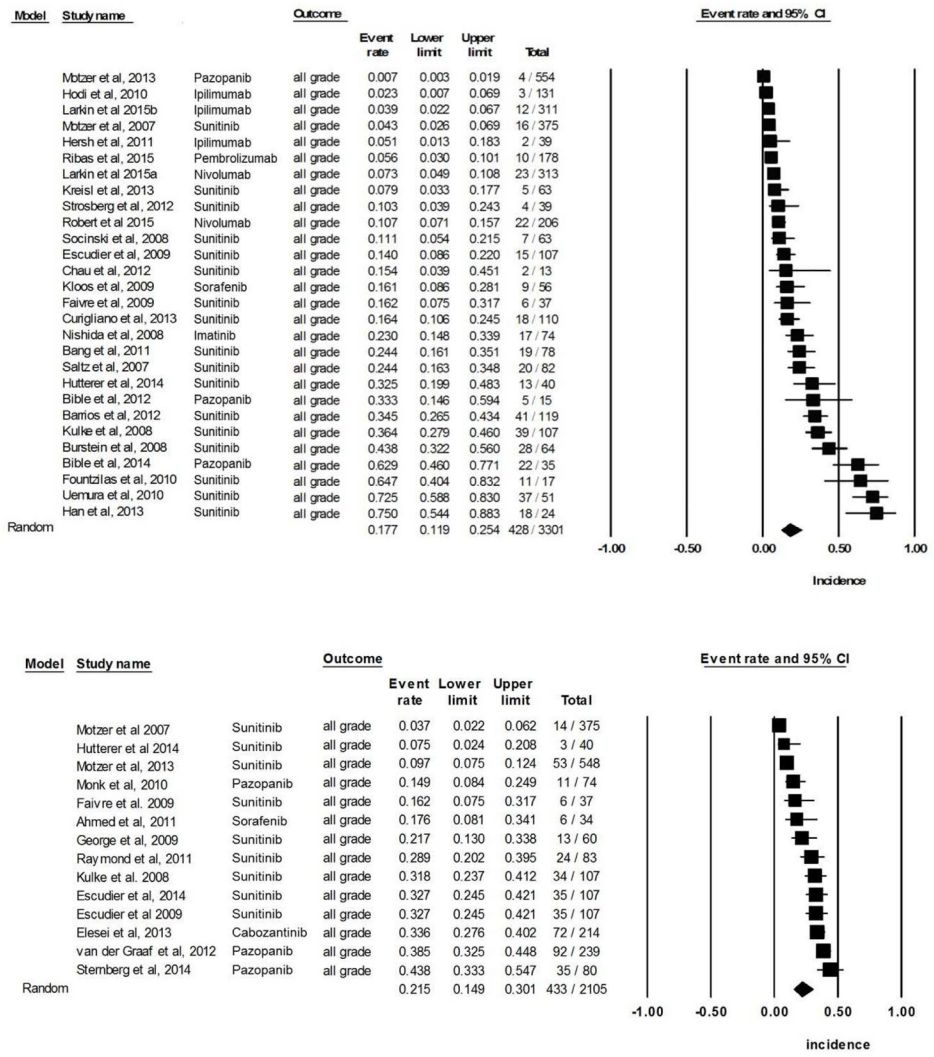

Figure 2.

Figure 2A. Incidence of all-grade targeted therapy-induced pigmentary changes in skin.

Figure 2B. Incidence of all-grade targeted therapy-induced pigmentary changes in hair.

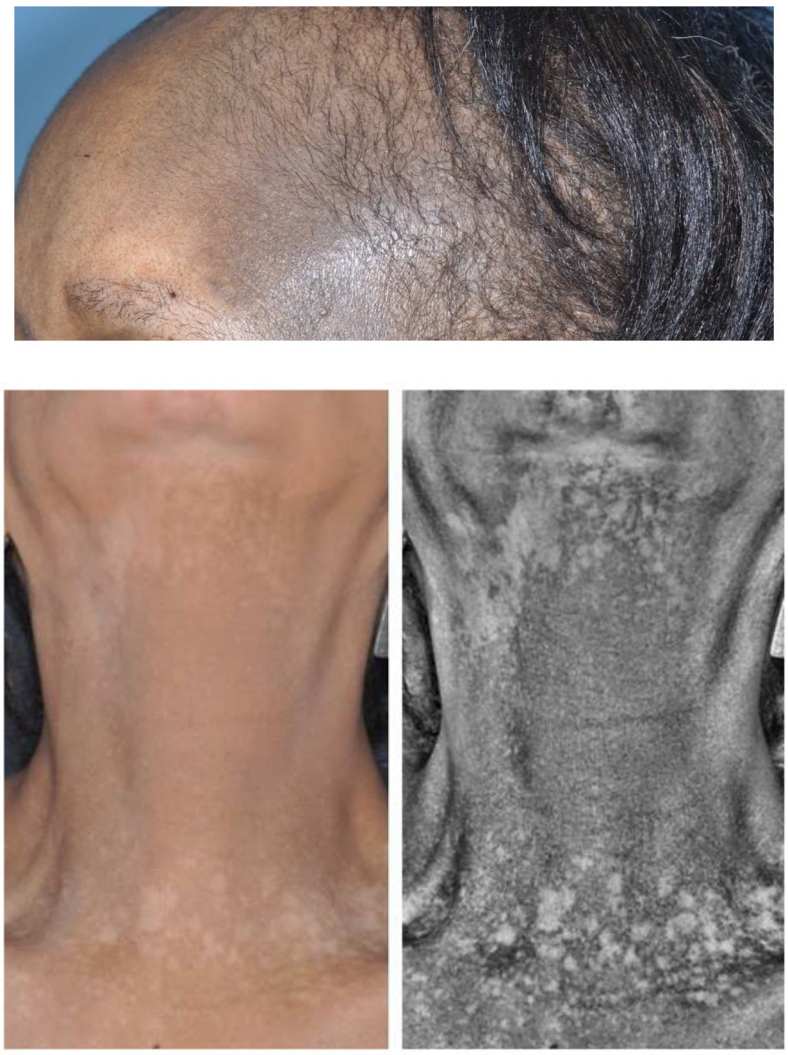

Figure 3.

Figure 3A. Gray-colored imatinib-induced hyperpigmentation predominantly on the face of a 65-year-old female with gastrointestinal stromal tumor.

Figure 3B. Well-defined asymptomatic depigmented macules (enhanced under Wood's light) predominantly on the face and neck in a 65-year-old female receiving MK-3475 (pembrolizumab) for melanoma.

Table 1

Incidence of all-grade pigmentary changes with approved targeted agents in monotherapy.

Drug	Primary molecular targets	Incidence of all-grade pigmentary changes (95% CI)	
		Skin	Hair
Cabozantinib[39]	VEGF-R1/-R2/-R3, Flt-3, MET, RET, KIT, AXL, TRKB, TEK, TIE-2	Not yet reported	33.6% (27.6%–40.2%)
Imatinib[11]	BCR-ABL, PDGFR-α/β, KIT	23.0% (14.8%–33.9%)	Not yet reported
Ipilimumab[12,35–36]	CTLA-4	3.6% (2.3%–5.8%)	Not yet reported
Nivolumab[37–38]	PD-1	8.8% (6.1%–12.7%)	Not yet reported
Pazopanib[13–14,32,39,43–44]	VEGF-R1/-R2/-R3, PDGFR-α/β, KIT, RAF	15.6% (0.7%–83.4%)	31.7% (18.9%–48.0%)
Pembrolizumab[40]	PD-1	5.6% (3.0%–10.1%)	Not yet reported
Sorafenib[15,33]	VEGF-R1/-R2/-R3, PDGFR-β, KIT, RET, RAF (CRAF & BRAF)	16.1% (8.6%–28.1%)	17.6% (8.1%–34.1%)
Sunitinib[16–31,34,41,45–46]	VEGF-R1/-R2/-R3, PDGFR, KIT, RET, CSF-1R, Flt-3	25.5% (17.0%–36.4%)	17.9% (10.5%–28.7%)

Table 2

Published case reports/series of pigmentary changes during treatment with targeted anticancer agents (n=54).

#	Dermatologic AE	Primary mechanism of action	Targeted agent	Number of cases
1. Skin change				
	Hyperpigmentation	EGFR inhibitor	Gefitinib[1]	2
		Bcr-abl inhibitor	Imatinib[2–8]	15
	Repigmentation	Bcr-abl inhibitor	Imatinib[9]	1
		JAK inhibitor	Ruxolitinib[10]	1
	Hypopigmentation	EGFR inhibitor	Iefitinib[11]	1
		Bcr-abl inhibitor(s)	Imatinib[5,12–19]	14
			Dasatinib[20–22]	3
		Immunomodulator	IL-2[23]	1
		VEGFR inhibitor(s)	Pazopanib[24]	1
			Sunitinib[25–26]	2
		BRAF inhibitor	Vemurafenib[27]	1
		PD-1 inhibitor	Pembrolizumab[28]	1
	Other dyschromias (blue/gray, yellow)	Bcr-abl inhibitor	Imatinib[29–31]	3
		VEGFR inhibitor	Sorafenib[32]	1
		EGFR/ VEGFR inhibitor	Vandetanib[33–34]	3
2. Hair change				
	Repigmentation	EGFR inhibitor	Erlotinib[35]	1
	Hypopigmentation	EGFR inhibitor	Cetuximab[36]	1
		Bcr-abl inhibitor(s)	Imatinib[37]	1
			Dasatinib[20–21,38–39]	4
		VEGFR inhibitor(s)	Pazopanib[24,40]	2
			Regorafenib[41]	1
			Sunitinib[25,42]	2
		PD-1 inhibitor	Pembrolizumab[28]	1

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#	Dermatologic AE	Primary mechanism of action	Targeted agent	Number of cases
3. Nail change				
	Hyperpigmentation	EGFR inhibitor	Gefitinib[43]	1
		Bcr-abl inhibitor	Imatinib[44–46]	3
	Other dyschromias (yellow)	mTOR inhibitor	Temsirolimus[47]	1
4. Mucosal change of hard palate				
	Other dyschromias	Bcr-abl inhibitor	Imatinib[5,29–31,44,46,48–54]	17