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

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***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 development of 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:*** A total of 8052 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% confidence interval [CI], 11.9-25.4) and 21.5% (95% CI, 14.9-30.1), respectively. The relative risk of all-grade 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 53 case reports/series (N = 75 patients), epidermal growth factor receptor and breakpoint cluster region–abelson inhibitors were the most common offending agents.

***Limitations:*** Potential under-reporting and variability in oncologists reporting these events.

***Conclusion:*** There is a significant risk of development of pigmentary changes during treatment with targeted anticancer therapies. Appropriate counseling and management are critical to minimize psychosocial impairment and deterioration in quality of life. ( J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.06.044.)

***Key words:*** cabozantinib; depigmentation; dyspigmentation; hyperpigmentation; hypopigmentation; imatinib; ipilimumab; nivolumab; pazopanib; pembrolizumab; pigmentary; repigmentation; sorafenib; sunitinib; vitiligo.

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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). Although systemic adverse events (AEs) characteristic of conventional cytotoxic agents (eg, myelosuppression, nausea, vomiting)[3] are typically not encountered, dermatologic AEs (affecting the skin, hair, nails, and 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 and/or nail changes are some of the most commonly encountered targeted therapy–induced dermatologic AEs.[5] Although not life threatening, they can negatively affect patients' HRQoL and impair psychosocial functioning and activities of daily living.[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.

**CAPSULE SUMMARY**

- Dermatologic adverse events are a common occurrence in patients receiving targeted anticancer medications.
- There is an increased risk of development of targeted therapy–induced pigmentary changes, but the causal agents and specific risks are not well described.
- Understanding targeted therapy–induced pigmentary changes is critical for appropriate management to improve this psychosocially impactful adverse event.

## METHODS

### Data source

We searched all targeted anticancer agents (n = 64) approved by the US Food and Drug Administration (www.FDA.gov) in January 2017 (Appendix I; available at http://www.jaad.org). A PubMed search was conducted using the generic name of targeted agents (eg, afatinib) as the key word. The search was limited to phase II and phase III randomized clinical trials (RCTs) and nonrandomized clinical trials published in English (from January 1998 through January 2017). We also reviewed abstracts and virtual meeting presentations (from January 2004 through January 2017) posted on the American Society of Clinical Oncology website to further identify relevant clinical trials. In addition, an independent search on the Web of Science database was 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 US Food and Drug Administration approves targeted therapies at a specific dose in the treatment of cancer. Therefore, we excluded clinical trials using drugs at unapproved doses (eg, phase I studies) 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, or nails. Studies that met the following criteria were selected for final analysis: (1) prospective phase II or III clinical trial 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 end points 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 (version 2.0), or the Common Terminology Criteria for AEs (versions 3.0 and v4.0). The grading of dpAEs in the skin in version 2.0 is described as follows: grade 0, none; grade 1, localized; and grade 2, generalized. In version 3.0, the description was updated to hyperpigmentation and hypopigmentation, as

*Abbreviations used:*

| | |
|---|---|
| AE: | adverse event |
| Bcr-abl: | breakpoint cluster region—abelson |
| BSA: | body surface area |
| CI: | confidence interval |
| dpAE: | dermatologic pigmentary adverse event |
| RR: | relative risk |
| RCT: | randomized controlled trial |

follows: grade 1, slight or localized, and grade 2, marked or generalized. Version 4.0 further stratifies hyperpigmentation and hypopigmentation by body surface area (BSA) involvement as follows: grade 1, covering less than 10% of the BSA and having no psychosocial impact, and grade 2, covering more than 10% of the BSA and associated psychosocial impact. However, none of the studies in our meta-analysis utilized the Common Terminology Criteria for AEs, version 4.0. 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 by using Comprehensive Meta-Analysis program (version 2.0, Biostat, Englewood, NJ). The numbers of patients with pigmentary AEs in the treatment and control groups (as applicable) were 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 models 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 $P$ values of the Cochran $Q$ statistic less than 0.1, the assumption of homogeneity was deemed invalid, and the random-effects model was used after exploring the cause of heterogeneity. Barring this phenomenon, both the fixed-effects and random-effects models were reported. A 2-tailed $P$ value less than .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 (J.D.) reviewed all the identified manuscripts and extracted the following data onto an Excel spreadsheet: age, sex, 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, and year of publication.

## RESULTS

### Search results

Our literature search yielded a total of 7604 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, 8052 patients (controls [n = 3648] and drug [n = 4404]) were analyzed across trials using cabozantinib, imatinib, ipilimumab, nivolumab, pazopanib, pembrolizumab, sorafenib, or sunitinib, which represented the 8 major drugs of the 64 (12.5%) included in the search. The data were analyzed separately for dpAEs of the skin and hair.

### Incidence of all-grade pigmentary changes in skin

Data for all-grade dpAEs of skin were available for 6538 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: $Q = 416.4$, $I^2 = 93.5$, $P < .001$) (Fig 2, *A*). The lowest incidence, 0.7%, was noted in the pazopanib arm (n = 554) of a randomized, open-label, phase III trial involving patients with metastatic renal cell carcinoma.[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 drugwise summary incidences of all-grade pigmentary changes are provided in Table I.[11-31,34-46]

### Incidence of all-grade pigmentary changes in hair

In all, we identified 14 clinical trials (involving 3319 evaluable patients) that reported hair color

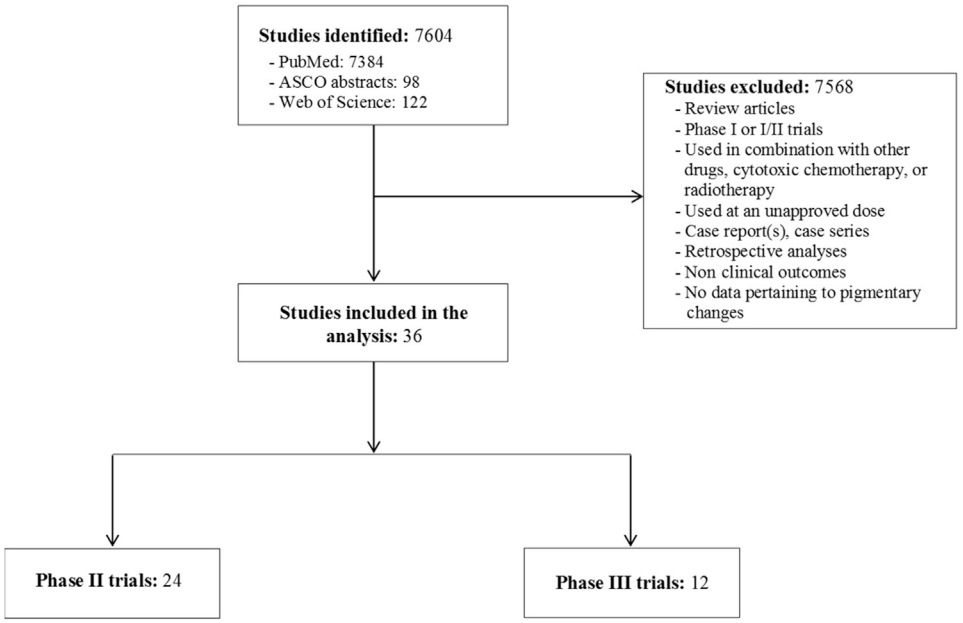


**Fig 1.** Selection process for studies included in the meta-analysis. *ASCO*, American Society of Clinical Oncology.

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, $P < .001$) (Fig 2, *B*). The lowest incidence, 3.7%, was noted in the sunitinib arm (n = 375) of a randomized, double-blinded, phase III trial involving patients with metastatic renal cell carcinoma[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

To estimate the relative risk (RR) of these changes in patients receiving targeted therapies as compared with placebo, a pooled meta-analysis was performed by using RCTs as the control arm. All-grade skin pigmentary changes were noted in 428 of 3301 patients receiving targeted therapies[11-31,35-41] as opposed to in none of 360 patients who received best supportive care alone.[41] The calculated overall RR for all-grade changes was 93.7 (95% CI, 5.86-1497.164; $P < .001$), according to the random-effects model. The calculated high-grade RR was 2.371 (95% CI, 0.134-42.003; $P$ = .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 the 187of 536 patients receiving targeted therapies, as compared with those in the 5 of 314 patients who received best supportive care alone. The calculated RR was 20.1 (95% CI, 8.35-48.248; $P < .001$) according to the fixed-effects model. The calculated high-grade RR was 2.134 (95% CI, 0.224-20.355; $P$ = .510).

## Case reports and case series

Our search strategy yielded 53 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 8 were case series (n = 25 patients), with single-case reporting representing the majority (45 of 53 patients [85%]). Given the case-level nature of the reports, we conducted a pooled analysis and provided a summary of our findings (Table II[S1-S53])—the raw data pertaining to all cases, their description, and references are provided in Appendix II (available at http://www.jaad.org).

The mean patient age was 49.8 years (range, 8-83), with a slight preponderance of female patients (39 of 70 [55.7%]). The time to onset ranged from "immediately" to up to 10 years after initiation of treatment, and most reports (n = 29 of 53 [54.7%]) pertained to imatinib (43 of 70 patients [61.4%]). Accordingly, nearly half of the case patients (33 of 70 [47.1%]) had been treated for chronic myeloid leukemia. Importantly, only 6 of 70 case patients (8.6%) experienced dose alterations due to dpAEs.

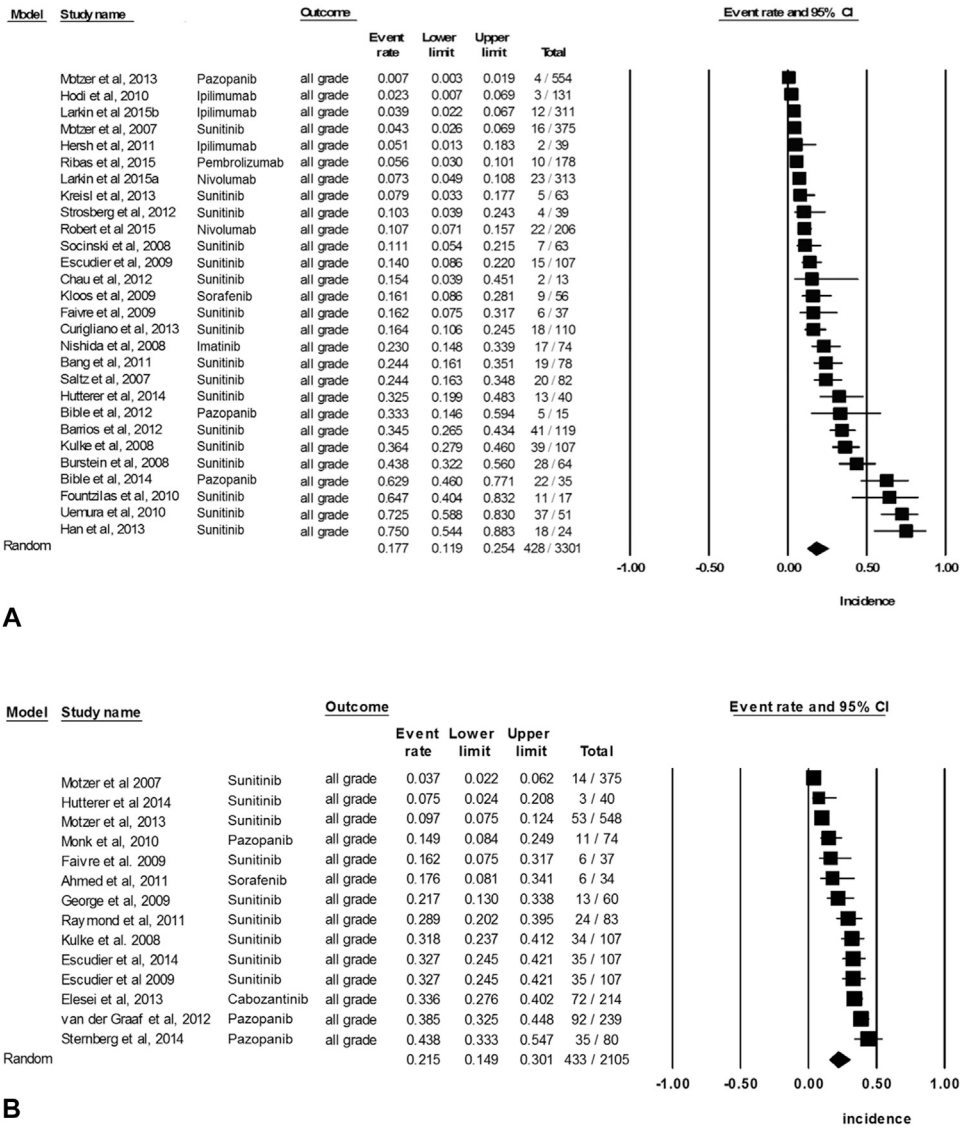


**Fig 2. A**, Incidence of all-grade targeted therapy—induced pigmentary changes in skin. **B**, Incidence of all-grade targeted therapy—induced pigmentary changes in hair. *CI*, Confidence interval.

The skin appeared to be the most commonly affected site, followed by the mucosa, hair, and nails. Although generalized skin involvement did occur (n = 10), localized affliction of the face (n = 36), trunk (n = 10), hands and/or 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 of 50 cases (22.0%); resolution in 7 of 50 (14.0%), and persistence in 4 of 50 cases (8.0%). The information pertaining to reversibility was not described in the rest. The breakpoint cluster region—abelson inhibitor imatinib was responsible for the majority of skin-related dpAEs in this pooled analysis of cases. In cases in which hair was affected, scalp hair involvement predominated (10 of 13 cases [76.9%]), although virtually all hair-bearing areas appear susceptible; inhibitors of the breakpoint cluster region—abelson and vascular endothelial growth factor receptor were the most common culprits. Nail dpAEs included hyperpigmentation and yellow discoloration in a total of 5 cases. Mucosal dpAEs were seen exclusively 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

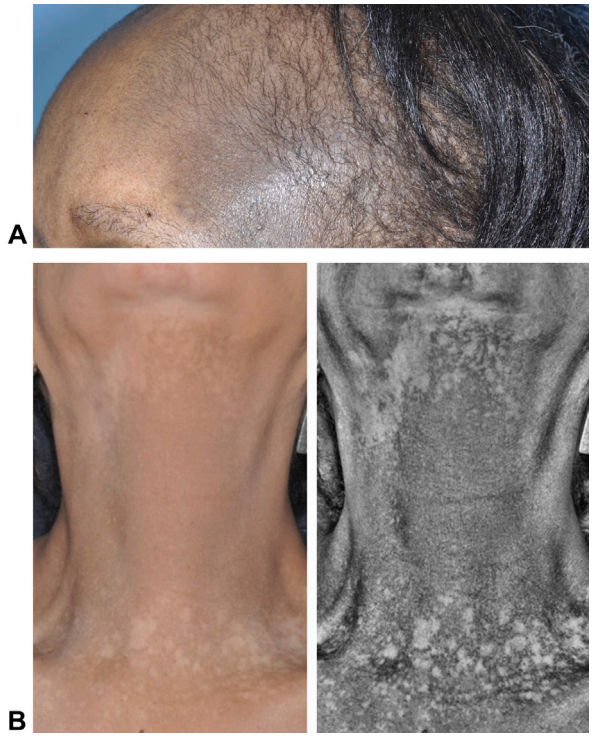


**Fig 3. A**, Gray imatinib-induced hyperpigmentation predominantly on the face of a 65-year-old woman with gastrointestinal stromal tumor. **B**, Well-defined asymptomatic depigmented macules (enhanced under Wood's light) predominantly on the face and neck in a 65-year-old woman receiving MK-3475 (pembrolizumab) for melanoma.

reviewing pertinent case reports/series. We found that the overall incidence of dpAEs in patients exposed to targeted anticancer therapies is high (17.7% in the case of skin, 21.5% in the case of hair). 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 have demonstrated that imatinib may decrease skin pigmentation by inhibiting tyrosinase activity, likely through blockade of the c-Kit pathway and platelet-derived growth factor inhibition.[50] Interestingly, paradoxical cases of imatinib-associated hyperpigmentation have also been described,[51-53] although the mechanisms underlying these differential reactions remain unclear (Fig 3, *A*).

Similarly, dpAEs associated with multikinase 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 nonselective multikinase inhibitors, cabozantinib, pazopanib, sorafenib, and sunitinib are probably associated with *c-kit* inhibition, although 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 cytotoxic T-lymphocyte antigen-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 (Fig 3, *B*).[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 on symptom management, because termination of drug exposure typically leads to resolution of the dpAEs. Patients should also be advised to use appropriate ultraviolet 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 health care providers and institutions, which could have affected safety reporting in clinical trials. Therefore, these inconsistencies may have resulted in the under-reporting, and consequently, underestimation of the incidence of targeted anticancer therapy–induced dpAEs.

The study of AEs, especially dermatologic, has 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 patients with cancer. This phenomenon is of particular importance because these events bear the potential to negatively affect 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,

**Table I.** 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[42] | 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-$\alpha/\beta$, 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-$\alpha/\beta$, 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-$\beta$, KIT, RET, RAF (CRAF and 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%) |

*AXL*, AXL receptor tyrosine kinase; *BCR-ABL*, breakpoint cluster region—abelson; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *CI*, confidence interval; *CRAF*, c-raf proto-oncogene, serine/threonine kinase; *CSF-1R*, colony stimulating factor 1 receptor; *CTLA-4*, cytotoxic T-lymphocyte antigen-4; *Flt*, fms-like tyrosine kinase; *KIT*, KIT protein; *MET*, mesenchymal-epithelial transition factor; *PD-1*, programmed cell death 1; *PDGFR*, platelet-derived growth factor receptor; *RAF*, rapidly accelerated fibrosarcoma; *RET*, rearranged during transfection; *TEK*, tyrosine kinase endothelial; *TIE*, tyrosine kinase with immunoglobulin-like and EGF-like domains; *TRKB*, tropomyosin receptor kinase B; *VEGF-R*, vascular endothelial growth factor receptor.

**Table II.** Published case reports/series of pigmentary changes during treatment with targeted anticancer agents (N = 53)

| Dermatologic AE | Primary mechanism of action | Targeted agent | No. of cases |
|---|---|---|---|
| Skin change | | | |
| Hyperpigmentation | EGFR inhibitor | Gefitinib[S1] | 2 |
| | Bcr-abl inhibitor | Imatinib[S2-S7] | 10 |
| Repigmentation | Bcr-abl inhibitor | Imatinib[S8] | 1 |
| | JAK inhibitor | Ruxolitinib[S9] | 1 |
| Hypopigmentation | EGFR inhibitor | Gefitinib[S10] | 1 |
| | Bcr-abl inhibitor(s) | Imatinib[S5,S11-S18] | 14 |
| | | Dasatinib[S19-S21] | 3 |
| | Immunomodulator | IL-2[S22] | 1 |
| | VEGFR inhibitor(s) | Pazopanib[S23] | 1 |
| | | Sunitinib[S24,S25] | 2 |
| | BRAF inhibitor | Vemurafenib[S26] | 1 |
| | PD-1 inhibitor | Pembrolizumab[S27] | 1 |
| Other dyschromias (blue/gray, yellow) | Bcr-abl inhibitor | Imatinib[S28-S30] | 3 |
| | VEGFR inhibitor | Sorafenib[S31] | 1 |
| | EGFR/VEGFR inhibitor | Vandetanib[S32,S33] | 3 |
| Hair change | | | |
| Repigmentation | EGFR inhibitor | Erlotinib[S34] | 1 |
| Hypopigmentation | EGFR inhibitor | Cetuximab[S35] | 1 |
| | Bcr-abl inhibitor(s) | Imatinib[S36] | 1 |
| | | Dasatinib[S19,S20,S37,S38] | 4 |
| | VEGFR inhibitor(s) | Pazopanib[S23,S39] | 2 |
| | | Regorafenib[S40] | 1 |
| | | Sunitinib[S24,S41] | 2 |
| | PD-1 inhibitor | Pembrolizumab[S27] | 1 |
| Nail change | | | |
| Hyperpigmentation | EGFR inhibitor | Gefitinib[S42] | 1 |
| | Bcr-abl inhibitor | Imatinib[S43-S45] | 3 |
| Other dyschromias (yellow) | mTOR inhibitor | Temsirolimus[S46] | 1 |
| Mucosal change of hard palate | | | |
| Other dyschromias | Bcr-abl inhibitor | Imatinib[S5,S28-S30,S43,S45,S47-S53] | 17 |

*AE*, Adverse event; *Bcr-abl*, breakpoint cluster region—abelson; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *EGFR*, epidermal growth factor receptor; *JAK*, Janus kinase; *mTOR*, mammalian target of rapamycin; *PD-1*, programmed cell death 1; *VEGFR*, vascular endothelial growth factor receptor.

suggesting that these AEs could be increasingly encountered. Therefore, there is an urgent need to educate patients and health care 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.

**REFERENCES**

1. Soreide K, Berg M, Skudal BS, Nedreboe BS. Advances in the understanding and treatment of colorectal cancer. *Discov Med*. 2011;12:393-404.
2. Ricciardi S, Tomao S, de Marinis F. Toxicity of targeted therapy in non-small-cell lung cancer management. *Clin Lung Cancer*. 2009;10:28-35.
3. Vokes EE, Chu E. Anti-EGFR therapies: clinical experience in colorectal, lung, and head and neck cancers. *Oncology (Williston Park)*. 2006;20:15-25.
4. Jost M, Kari C, Rodeck U. The EGF receptor, an essential regulator of multiple epidermal functions. *Eur J Dermatol*. 2000;10:505-510.
5. Balagula Y, Lacouture ME, Cotliar JA. Dermatologic toxicities of targeted anticancer therapies. *J Support Oncol*. 2010;8:149-161.
6. Wagner LI, Berg SR, Gandhi M, et al. The development of a functional assessment of cancer therapy (FACT) questionnaire to assess dermatologic symptoms associated with epidermal growth factor receptor inhibitors (FACT-EGFRI-18). *Support Care Cancer*. 2013;21:1033-1041.
7. Rosen AC, Case EC, Dusza SW, et al. Impact of dermatologic adverse events on quality of life in 283 cancer patients: a questionnaire study in a dermatology referral clinic. *Am J Clin Dermatol*. 2013;14:327-333.
8. Boone SL, Rademaker A, Liu D, Pfeiffer C, Mauro DJ, Lacouture ME. Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. *Oncology*. 2007;72:152-159.
9. Ensslin CJ, Rosen AC, Wu S, Lacouture ME. Pruritus in patients treated with targeted cancer therapies: systematic review and meta-analysis. *J Am Acad Dermatol*. 2013;69(5):708-720.
10. Valentine J, Belum VR, Duran J, et al. Incidence and risk of xerosis with targeted anticancer therapies. *J Am Acad Dermatol*. 2015;72:656-667.
11. Nishida T, Shirao K, Sawaki A, et al. Efficacy and safety profile of imatinib mesylate (ST1571) in Japanese patients with advanced gastrointestinal stromal tumors: a phase II study (STI571B1202). *Int J Clin Oncol*. 2008;13:244-251.
12. Hersh EM, O'Day SJ, Powderly J, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naïve patients with advanced melanoma. *Invest New Drugs*. 2011;29:489-498.
13. Bible KC, Suman VJ, Molina JR, et al. A multicenter phase II trial of pazopanib in metastatic and progress medullary thyroid carcinoma: MC057H. *J Clin Endocrinol Metab*. 2014;99(5):1687-1693.
14. Bible KC, Suman VJ, Menefee ME, et al. A multiinstitutional phase II trial of pazopanib monotherapy in advanced anaplastic thyroid cancer. *J Clin Endocrinol Metab*. 2012;97:3179-3184.
15. Kloos RT, Ringel MD, Knopp MV, et al. Phase II trial of sorafenib in metastatic thyroid cancer. *J Clin Oncol*. 2009;27:1675-1684.
16. Curigliano G, Pivot X, Cortes J, et al. Randomized phase II study of sunitinib versus standard of care for patients with previously treated advanced triple-negative breast cancer. *Breast*. 2013;22:650-656.
17. Han JY, Kim HY, Lim KY, et al. A phase II study of sunitinib in patients with relapsed or refractory small cell lung cancer. *Lung Cancer*. 2013;79:137-142.
18. Strosberg JR, Weber JM, Choi J, et al. A phase II clinical trial of sunitinib following hepatic transarterial embolization for metastatic neuroendocrine tumors. *Ann Oncol*. 2012;23(9):2335-2341.
19. Kreisl TN, Smith P, Sul J, et al. Continuous daily sunitinib for recurrent glioblastoma. *J Neurooncol*. 2013;111:41-48.
20. Chau NG, Hotte SJ, Chen EX, et al. A phase II study of sunitinib in recurrent and/or metastatic adenoid cystic carcinoma (ACC) of the salivary glands: current progress and challenges in evaluating molecularly targeted agents in ACC. *Ann Oncol*. 2012;23:1562-1570.
21. Barrios CH, Hernandez-Barajas D, Brown MP, et al. Phase II trial of continuous once-daily dosing of sunitinib as first-line treatment in patients with metastatic renal cell carcinoma. *Cancer*. 2012;118:1252-1259.
22. Bang YJ, Kang YK, Kang WK, et al. Phase II study of sunitinib as second-line treatment for advanced gastric cancer. *Invest New Drugs*. 2011;29:1449-1458.
23. Uemura H, Shinohara N, Yuasa T, et al. A phase II study of sunitinib in Japanese patients with metastatic renal cell carcinoma: insights into treatment, efficacy, and safety. *Jpn J Clin Oncol*. 2010;40(3):194-202.
24. Escudier B, Roigas J, Gillessen S, et al. Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27:4068-4075.
25. Faivre S, Raymond E, Boucher E, et al. Safety and efficacy of suntinib in patients with advanced hepatocellular carcinoma: an open-label, multicentre, phase II study. *Lancet Oncol*. 2009;10:794-800.
26. Kulke MH, Lenz HJ, Meropol NJ, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol*. 2008;26:3403-3410.
27. Burstein HJ, Elias AD, Rugo HS, et al. Phase II study of sunitinib malate, on oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol*. 2008;26:1810-1816.
28. Socinski MA, Novella S, Brahmer JR, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. *J Clin Oncol*. 2008;26:650-656.
29. Saltz LB, Rosen LS, Marshall JL, et al. Phase II trial of sunitinib in patients with metastatic colorectal cancer after failure of standard therapy. *J Clin Oncol*. 2007;25:4793-4799.
30. Hutterer M, Nowosielski M, Haybaeck J, et al. A single-arm phase II Austrian/German multicenter trial on continuous daily sunitinib in primary glioblastoma at first recurrence (SURGE 01-07). *Neuro Oncol*. 2014;16(1):92-102.
31. Fountzilas G, Fragkoulidi A, Kalogera-Fountzila A, et al. A phase II study of sunitinib in patients with recurrent and/or metastatic non-nasopharyngeal head and neck cancer. *Cancer Chemother Pharmacol*. 2010;65:649-660.

32. Monk BJ, Mas Lopez L, Zarba JJ, et al. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. *J Clin Oncol*. 2010;28(22):3562-3569.
33. Ahmed M, Barbachano Y, Riddell A, Hickey J, Newbold KL, Viros A. Analysis of the efficacy and toxicity of sorafenib in thyroid cancer: a phase II study in a UK based population. *Eur J Endocrinol*. 2011;165(2):315-322.
34. George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. *J Clin Oncol*. 2009;27(19):3154-3160.
35. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
36. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015; 372(26):2521-2532.
37. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.
38. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without *BRAF* mutation. *N Engl J Med*. 2015;372(4):320-330.
39. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369:711-731.
40. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. 2015;16:908-918.
41. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356:115-124.
42. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol*. 2013; 31(29):3639-3646.
43. Sternberg CN, Davis ID, Deen KC, Sigal E, Hawkins RE. An open-label extension study to evaluate safety and efficacy of pazopanib in patients with advanced renal cell carcinoma. *Oncology*. 2014;87(6):342-350.
44. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012; 379(9829):1879-1886.
45. Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES study. *J Clin Oncol*. 2014;32(14):1412-1418.
46. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513.
47. Robert C, Sibaud V, Mateus C, Cherpelis BS. Advances in the management of cutaneous toxicities of targeted therapies. *Semin Oncol*. 2012;39:227-240.
48. Tsao AS, Kantarjian H, Cortes J, O'Brien S, Talpaz M. Imatinib mesylate causes hypopigmentation in the skin. *Cancer*. 2003; 98:2483-2487.
49. Cario-Andre M, Ardilouze L, Pain C, Gauthier Y, Mahon FX, Taieb A. Imatinib mesilate inihibits melanogenesis in vitro. *Br J Dermatol*. 2006;155:493-494.
50. Buchdunger E, Cioffi CL, Law N, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. *J Pharmacol Exp Ther*. 2000;295(1):139-145.
51. Heidary N, Naik H, Burgin S. Chemotherapeutic agents and the skin: an update. *J Am Acad Dermatol*. 2008;58:545-570.
52. Basso FG, Boer CC, Correa ME, et al. Skin and oral lesions associated to imatinib mesylate therapy. *Support Care Cancer*. 2009;17:465-468.
53. McPherson T, Sherman V, Turner R. Imatinib-associated hyperpigmentation, a side effect that should be recognized. *J Eur Acad Dermatol Venereol*. 2009;23:82-83.
54. Picardo M, Cardinali G. The genetic determination of skin pigmentation: KITLG and the KITLG/c-Kit pathway as key players in the onset of human familial pigmentary diseases. *J Invest Dermatol*. 2011;131:1182-1185.
55. Spritz RA. The molecular basis of human piebaldism. *Pigment Cell Res*. 1992;5:3403.
56. Grimes PE. New insights and new therapies in vitiligo. *JAMA*. 2005;293:730-735.
57. Tarhini A. Immune-mediated adverse events associated with ipilimumab CTLA-4 blockade therapy: the underlying mechanisms and clinical management. *Scientifica (Cairo)*. 2013; 2013:857519.
58. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012;30(21):2691-2697.
59. Pavlick AC, Ott PA, Kannan K, et al. Hair depigmentation as an indicator of a durable response to CTLA-4 therapy [abstract] *J Clin Oncol*. 2010;28(suppl 15):8571.
60. Hua C, Boussemart L, Mateus C, et al. Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. *JAMA Dermatol*. 2016;152(1):45-51.
61. Larsabal M, Marti A, Jacquemin C, et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo. *J Am Acad Dermatol*. 2017;76:863-870.

## APPENDIX I. LIST OF ALL TARGETED AGENTS SEARCHED FOR TO IDENTIFY STUDIES REPORTING DERMATOLOGIC PIGMENTARY ADVERSE EVENTS (N = 64)

Ado-trastuzumab emtansine
Afatinib dimaleate
Alectinib
Alemtuzumab
Atezolizumab
Axitinib
Belinostat
Bevacizumab
Blinatumomab
Bortezomib
Bosutinib
Brentuximab vedotin
Cabozantinib
Carfilzomib
Ceritinib
Cetuximab
Cobimetinib
Crizotinib
Dabrafenib
Daratumumab
Dasatinib
Dinutuximab
Elotuzumab
Erlotinib hydrochloride
Everolimus
Gefitinib
Ibrutinib
Idelalisib
Imatinib mesylate
Ipilimumab
Ixazomib
Lapatinib ditosylate
Lenvatinib
Necitumumab
Nilotinib
Nivolumab
Obinutuzumab
Ofatumumab
Olaparib
Olaratumab
Osimertinib
Palbociclib
Panitumumab
Panobinostat
Pazopanib hydrochloride
Pembrolizumab
Pertuzumab
Ponatinib
Ramucirumab
Regorafenib
Rituximab
Romidepsin
Ruxolitinib
Sorafenib tosylate
Sonidegib
Sunitinib malate
Temsirolimus
Trametinib
Trastuzumab
Vandetanib
Vemurafenib
Vismodegib
Vorinostat
Ziv-aflibercept

## APPENDIX II. PUBLISHED CASE REPORTS/SERIES OF PIGMENTARY CHANGES DURING TREATMENT WITH TARGETED ANTICANCER AGENTS (N = 53)

S1. Chang GC, Yang TY, Chen KC, Yin MC, Wang RC, Lin YC. Paronychia and skin hyperpigmentation induced by gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol*. 2004;22:4646-4647.
S2. Alexandrescu DT, Dasanu CA, Farzanmehr H, Kauffman CL. Persistent cutaneous hyperpigmentation after tyrosine kinase inhibition with imatinib for GIST. *Dermatol Online J*. 2008;14(7):7.
S3. Prasad N, Deshmukh C, Biswas G, Bakshi A, Sastry PS, Parikh PM. Dermatological toxicity of imatinib mesylate. *J Assoc Physicians India*. 2005;53:298.
S4. Hamza I, Gaies E, Kastalli E, Daghfous R, El Aidli S. Facial hyperpigmentation during imatinib therapy for gastrointestinal stromal tumor. *Therapie*. 2014;69:245-247.
S5. Singh N, Bakshi S. Imatinib-induced dental hyperpigmentation in childhood chronic myeloid leukemia. *J Pediatr Hematol Oncol*. 2007;29:208.
S6. Ghunawat S, Sarkar R, Garg VK. Imatinib induced melasma-like pigmentation: report of five cases and review of literature. *Indian J Dermatol Venereol Leprol*. 2016;82:409-412.
S7. Valizadeh N. Imatinib induced facial skin hyperpigmentation in a case of chronic myelogenous leukemia. *Shiraz E-Medical J*. 2011;12(3).
S8. Han H, Yu YY, Wang YH. Imatinib mesylate—induced repigmentation of vitiligo lesions in a patient with recurrent gastrointestinal stromal tumors. *J Am Acad Dermatol*. 2008;59:S80-S83.
S9. Harris JE, Rashighi M, Nguyen N, et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). *J Am Acad Dermatol*. 2016;74:370-371.
S10. Jalalat SZ, Cohen PR. Gefitinib-associated vitiligo: report in a man with parotid squamous cell carcinoma and review of drug-induced hypopigmentation. *Dermatol Online J*. 2013;19(10):4.
S11. Tsao AS, Kantarjian H, Cortes J, O'Brien S, Talpaz M. Imatinib mesylate causes hypopigmentation in the skin. *Cancer*. 2003;98:2483-2487.
S12. Raanani P, Goldman JM, Ben-Bassat I. Depigmentation in a chronic myeloid leukemia patient treated with STI-471. *J Clin Oncol*. 2002;20:869-870.

S13. Hasan S, DInh K, Lombardo F, Dawkins F, Kark J. Hypopigmentation in an African patient treated with imatinib mesylate: a case report. *J Natl Med Assoc*. 2003;95:722-724.
S14. Grossman WJ, Wilson DB. Hypopigmentation from imatinib mesylate (Gleevac). *J Pediatr Hematol Oncol*. 2004;26:214.
S15. Brazzelli V, Roveda E, Prestinarl F, et al. Vitiligo-like lesions and diffuse lightening of the skin in a pediatric patient treated with imatinib mesylate: a noninvasive colormetric assessment. *Pediatr Dermatol*. 2006;23:175-178.
S16. Legros L, Cassuto JP, Ortonne JP. Imatinib mesilate (Glivec): a systemic depigmenting agent for extensive vitiligo? *Br J Dermatol*. 2005;153:691-692.
S17. McPartlin S, Leach M. Loss of skin pigment caused by imatinib therapy. *Br J Haematol*. 2005;129:448.
S18. Cerchione C, Fabbricini R, Pane F, Luciano L. Vitiligo-like lesions in an adult patient treated with imatinib mesylate. *Leuk Res*. 2009;33(8):e104-e105.
S19. Brazzelli V, Grasso V, Barbaccia V, et al. Hair depigmentation and vitiligo-like lesions in a leukaemic paediatric patient during chemotherapy with dasatinib. *Acta Derm Venereol*. 2012;92:193-220.
S20. Fujimi A, Ibata S, Kanisawa Y, et al. Reversible skin and hair depigmentation during chemotherapy with dasatinib for chronic myeloid leukemia. *J Dermatol*. 2016;43:106-107.
S21. Boudadi K, Chugh R. Diffuse hypopigmentation followed by hyperpigmentation in an African American woman with hemangiopericytoma treated with dasatinib. *J Clin Diagn Res*. 2014;8(11):QD01-QD02.
S22. Gathings R, Lewallen R, Yosipovitch G. Immunotherapy-induced leukoderma from treatment of melanoma with IL-2: a case report and a review of the literature. *Acta Derm Venereol*. 2015; 95:197-200.
S23. Sideras K, Menefee ME, Burton JK, Erlichman C, Bible KC. Profound hair and skin hypopigmentation in an African American woman treated with the multi-targeted tyrosine kinase inhibitor pazopanib. *J Clin Oncol*. 2010;28:e312-e313.
S24. Hartmann JT, Kanz L. Sunitinib and periodic hair depigmentation due to temporary c-KIT inhibition. *Arch Dermatol*. 2008;144:1525-1526.
S25. Al Enazi MM, Kadry R, Mitwali H. Skin depigmentation induced by sunitinib treatment of renal cell carcinoma. *J Am Acad Dermatol*. 2009;61:905-906.
S26. Alonso-Castro L, Rios-Buceta L, Vano-Galvan S, Moreno C, Soria-Rivas A, Jaen P. Vitiligo in 2 patients receiving vemurafenib for metastatic melanoma. *J Am Acad Dermatol*. 2013;69(1):e28-e29.
S27. Wolner ZJ, Marghoob AA, Pulitzer MP, Postow MA, Marchetti MA. A case report of disappearing pigmented skin lesions associated with pembrolizumab treatment for metastatic melanoma. *Br J Dermatol*. 2017; http://dx.doi.org/10.1111/bjd.15354 [Epub ahead of print].
S28. Kagimoto Y, Mizuashi M, Kikuchi K, Aiba S. Lichenoid drug eruption with hyperpigmentation caused by imatinib mesylate. *Int J Dermatol*. 2014;53:e161-e162.
S29. Resende RG, Teixeira RGL, Vasconcelos FO, Silva MES, Abreu MHG, Gomez RS. Imatinib-associated hyperpigmentation of the palate in post-HSCT patient. *J Craniomaxillofac Surg*. 2012;40:e140-e143.
S30. Song HS, Kang HY. Imatinib mesylate-induced hyperpigmentation of the nose and palate. *Ann Dermatol*. 2014;26:532-533.
S31. Dasanu CA, Dutcher J, Alexandrescu DT. Yellow skin discoloration associated with sorafenib use for treatment of metastatic renal cell carcinoma. *South Med J*. 2007;100:328-330.
S32. Kong HH, Fine HA, Stern JB, Chanco Turner ML. Cutaneous pigmentation after photosensitivity induced by vandetanib therapy. *Arch Dermatol*. 2009;145:923-925.
S33. Brooks S, Linehan WM, Srinivasan R, Kong HH. Successful laser treatment of vandetanib-associated cutaneous pigmentation. *Arch Dermatol*. 2011;147:364-365.
S34. Cheng YP, Chen HJ, Chiu HC. Erlotinib-induced hair repigmentation. *Int J Dermatol*. 2014;53:e55-e57.
S35. Rodriguez NA, Ascaso FJ. Trichomegaly and poliosis of the eyelashes during cetuximab treatment of metastatic colorectal cancer. *J Clin Oncol*. 2011;29:e532-e533.
S36. Mariani S, Abruzzese E, Basciani S, et al. Reversible hair depigmentation in a patient treated with imatinib. *Leuk Res*. 2011;35(6):e64-e66.
S37. Sun A, Akin RS, Cobos E, Smith J. Hair depigmentation during chemotherapy with dasatinib, a dual Bcr-Abl/Src family tyrosine kinase inhibitor. *J Drugs Dermatol*. 2009;8:395-398.
S38. Samimi S, Chu E, Seykora J, et al. Dasatinib-induced leukotrichia in a patient with chronic myelogenous leukemia. *JAMA Dermatol*. 2013;149:637-639.
S39. Kobayashi E, Koyama T, Kobayashi K, Setsu N, Kawashima M, Kawai A. Reversible hair depigmentation in a Japanese female treated with pazopanib. *J Dermatol*. 2014;41:1021-1022.
S40. Sibaud V, Munsch C, Lamant L. Eruptive nevi and hair depigmentation related to regorafenib. *Eur J Dermatol*. 2015;25:85-86.
S41. Brzezniak C, Szabo E. Sunitinib-associated hair depigmentation. *N Engl J Med*. 2014;370:e27.
S42. Huan TC, Ho CL. Blue-black discoloration of the nails associated with gefitinib. *Acta Clin Belg*. 2011;66:72.
S43. Steele JC, Triantafyllou A, Rajlawat BP, Field EA. Oral mucosal hyperpigmentation and horizontal melanonychia caused by imatinib. *Clin Exp Dermatol*. 2012;37:432-447.
S44. Prabhash K, Biswas G, Prasad N, et al. Imatinib-induced nail hyperpigmentation in chronic myeloid leukemia. *Indian J Dermatol Venereol Leprol*. 2006;72:63-64.
S45. Mcpherson T, Sherman V, Turner R. Imatinib-associated hyperpigmentation, a side effect that should be recognized. *J Eur Acad Dermatol Venereol*. 2009;23:82-83.
S46. Peuvrel L, Quereux G, Brocard A, Saint-Jean M, Dreno B. Onychopathy induced by temsirolimus, a mammalian target of rapamycin inhibitor. *Dermatology*. 2012;224:204-208.
S47. Roeker LE, Wolanskyj AP. Imatinib-associated melanosis of the palate. *Am J Hematol*. 2014;89:564.
S48. Wong M, Sade S, Gilbert M, Klieb HB. Oral melanosis after tyrosine kinase inhibition with imatinib for chronic myelogenous leukemia: report of a case and review of the literature. *Dermatol Online J*. 2011;17(6):4.
S49. Li CC, Malik SM, Blaeser BF, et al. Mucosal pigmentation caused by imatinib: report of three cases. *Head Neck Pathol*. 2012;6:290-295.
S50. Lewis DM. Diffuse pigmentation of the palate. *J Okla Dent Assoc*. 2009;100(8):24-25.
S51. Khoo TL, Catalano A, Supple S, et al. Hyperpigmentation of the hard palate associated with imatinib therapy for chronic myeloid leukemia with a genetic variation in the proto-oncogene c-KIT. *Leuk Lymphoma*. 2013;54:186-188.
S52. Mattsson U, Halbritter S, Serikoff EM, Christerson L, Warfvinge G. Oral pigmentation in the hard palate associated with imatinib mesylate therapy: a report of three cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;111(5):e12-e16.
S53. Yu YH, Shere Y, Vigneswaran N. Oral and maxillofacial pathology case of the month. Palatal melanosis associated with imatinib mesylate therapy. *Tex Dent J*. 2012;129:764-765.