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Dermatologic adverse events in pediatric patients receiving targeted anticancer therapies: a pooled analysis

Viswanath Reddy Belum, MD^{#1}, Courtney Washington, BS^{#1,5}, Christine A. Pratilas, MD², Vincent Sibaud, MD³, Franck Boralevi, MD⁴, and Mario E. Lacouture, MD^{1,*}

¹Department of Dermatology, Memorial Sloan Kettering Cancer Center, New York, NY USA

²Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, NY USA

³Department of Dermatology, Institut Claudius Regaud, Institut Universitaire Cancer Toulouse-oncopole, Toulouse, France

⁴Unité de Dermatologie Pédiatrique, Hôpital Pellegrin-enfants, Place Amélie Raba-Léon, 33076 Bordeaux Cedex, France

⁵Philadelphia College of Osteopathic Medicine, Suwanee, GA, USA

These authors contributed equally to this work.

Abstract

BACKGROUND—The dermatologic adverse events (AEs) of various molecularly targeted therapies are well-described in adult cancer patients. Little has been reported on the incidence and clinical presentation of such AEs in pediatric patients with cancer. To address this gap, we analyzed the dermatologic AEs reported across clinical trials of targeted anticancer therapies in pediatric patients.

METHODS—We conducted an electronic literature search (PubMed, American Society of Clinical Oncology annual meetings' abstracts, ClinicalTrials.gov, NCI's Pediatric Oncology Branch webpage) to identify clinical trials involving targeted anticancer therapies that reported dermatologic AEs in their safety data. Studies were limited to the pediatric population, monotherapy trials (oncology), and English language publications.

RESULTS—Pooled data from 19 clinical studies investigating 11 targeted anticancer agents (alemtuzumab, rituximab, imatinib, dasatinib, erlotinib, vandetanib, sorafenib, cabozantinib, pazopanib, everolimus, and temsirolimus) were analyzed. The most frequently encountered dermatologic AEs were rash (127/660; 19%), xerosis (18/100; 18%), mucositis (68/402; 17%) and

*Correspondence to: Mario E. Lacouture, MD, Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 60th Street Outpatient Center, Suite 407, Room 4312, 16 East 60th St, New York, NY 10022; Phone: (646) 888-6014 | Fax: (646) 227-7274 | lacoutum@mskcc.org.

CONFLICT OF INTEREST STATEMENT

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pruritus (12/169; 7%). Other AEs included pigmentary abnormalities of the skin/hair (13%), hair disorders (trichomegaly, hypertrichosis, alopecia and madarosis; 14%), urticaria (7%), palmoplantar erythrodysesthesia (7%), erythema, acne, purpura, skin fissures, other 'unknown skin changes', exanthem, infection, flushing, telangiectasia, and photosensitivity.

CONCLUSION—This study describes the dermatologic manifestations of targeted anticancer therapy-related AEs in the pediatric population. Since these AEs are often associated with significant morbidity, it is imperative that pediatric oncologists be familiar with their recognition and management, to avoid unnecessary dose modifications and/or termination, and to prevent impairments in patients' quality of life.

Keywords

adverse events; dermatologic; mucositis; pediatric; pruritus; rash; targeted therapies

INTRODUCTION

Significant advances in cancer biology have informed our understanding of oncogenic pathways and the underlying mechanisms that drive cancer and its spread. Consequently, several molecularly targeted therapies have been developed and have received regulatory approval for use in the treatment of various cancers. Their benefit in terms of improved survival rates has been demonstrated mostly in adult cancer patients, prompting investigators to explore their utility in the pediatric population. The efficacy and safety of these agents in children however, have not been thoroughly established. Moreover, the adverse events (AEs) may be different in children and adolescents than in adults, due to the overlap between developmental and oncogenic pathways and the propensity for long-term effects in childhood survivors [1, 2].

The emerging AE profile of targeted anticancer therapies differs from that of cytotoxic chemotherapy. Nevertheless, the potential to affect dose intensity remains significant. The latter is particularly true of dermatologic AEs, examples of which include but are not limited to rashes, xerosis, urticaria, pruritus, mucositis, alopecia, proliferative skin lesions, skin/hair dyspigmentation, and palmoplantar erythrodysesthesia (PPE; *syn.* Hand-foot syndrome [HFS], hand-foot-skin reaction [HFSR]) [3]. Although not life-threatening, these AEs bear the potential to entail serious impairments in patients' quality of life [4, 5], and dose modifications or discontinuation of anticancer therapy, all of which may affect clinical outcomes. Therefore, a comprehensive understanding and working knowledge of these issues is of paramount importance, given that many of the targeted agents approved in adult cancer patients are being used in pediatric clinical trials or off-label [6]. In the present study, we analyzed dermatologic AEs extracted from pediatric clinical trials evaluating targeted agents currently marketed in the treatment of cancer. Our aim is to provide the oncology healthcare provider, an overview of the dermatologic AEs associated with targeted anticancer therapies.

METHODS

Data source and search strategy

The PubMed, American Society of Clinical Oncology annual meetings' online abstracts database (asco.org), clinical trials registry website (ClinicalTrials.gov), and clinical trials listed on the National Cancer Institute-Center for Cancer Research' Pediatric Oncology branch homepage [7] were searched (through June 2014), to identify pediatric monotherapy trials investigating a targeted anticancer agent. The PubMed database search was conducted by combining two concepts—the drug name (code/generic/United States [U.S.] brand names), the operator 'AND', and a validated search filter to identify pediatric studies [8], as follows: (code name OR generic name OR U.S. brand name) AND (Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*). The following drugs were included in the search: ado-trastuzumab emtansine, afatinib, alemtuzumab, axitinib, bevacizumab, bortezomib, bosutinib, brentuximab, cabozantinib, carfilzomib, cetuximab, crizotinib, dabrafenib, dasatinib, erlotinib, everolimus, ibrutinib, imatinib, ipilimumab, nilotinib, ofatumumab, panitumumab, pazopanib, ponatinib, regorafenib, rituximab, ruxolitinib, sorafenib, sunitinib, temsirolimus, trametinib, trastuzumab, vandetanib, vemurafenib, and vismodegib. In addition, the FDA website was accessed to record targeted agents approved for the treatment of cancer in adults and children. Informed consent for photography was properly documented.

Study selection

We included clinical studies and phase 0-III clinical trials in the analysis only if they clearly reported dermatologic AEs in their safety data. Publications were evaluated to make sure that the study population was children, and that cancer was being treated. The identified records were then analyzed to determine if the targeted agent was used in monotherapy; studies involving any combination/sequential therapies/modalities were excluded. The retrieved records were cross-checked for any subsequently updated publications, and duplicates were discarded. We included articles published only in English. The selection process for studies included in the analysis is depicted in Figure 1.

From each report, the following details were extracted: drug investigated, name of the first author, year of publication/reporting of trial results, dosing details, tumor type, number of patients enrolled and treated, and study type (e.g., trial phase). Information pertaining to the dermatologic AEs was extracted from the safety data reported in each publication. Since the clinical severity grade reporting was not consistent, we recorded only the all-grade AE data.

RESULTS

Our electronic database search strategy yielded 2,126 potentially relevant records pertaining to cancer in pediatric patients. We retained 19 records that met our selection criteria, including those reporting dermatologic AEs in their safety data. Among those, ten were phase I or I/II trials [9-18], six were phase II trials [19-24], one was a phase III trial [25], one was an exploratory phase 0 trial [26], and one was a retrospective efficacy study [27]. One phase I trial of bevacizumab (vascular endothelial growth factor [VEGF]-A inhibitor) was not included in the analysis because the safety data did not include the number of patients experiencing AEs (only the number of events was reported) [28]. A majority of the drugs investigated in these trials were small molecule inhibitors of oncogenic pathways: imatinib/dasatinib (Bcr-abl), erlotinib (epidermal growth factor receptor, EGFR), vandetanib (EGFR/VEGF receptor [VEGFR]), sorafenib/cabozantinib/pazopanib (VEGFR/platelet-derived growth factor receptor [PDGFR]), and everolimus/temsirolimus (mechanistic target of rapamycin [mTOR]). Monoclonal antibodies to CD52 (alemtuzumab), CD20 (rituximab), and VEGF-A (bevacizumab) were investigated in one trial each. Since our aim was to provide an overview of the dermatologic AEs in pediatric patients with cancer, and because the individual trials or events were not a large enough sample size, we pooled the data across all trials in our analysis.

Patient and Clinical Trial Characteristics

Overall, 955 patients from a total of 19 clinical trials (including one retrospective efficacy study) were included. The key parameters of each trial are shown in Table I. Individual (baseline) characteristics of patients differed according to the enrollment criteria across various clinical trials and the cancers investigated. Similarly, the targeted agent used and the dosing also varied by the phase of the clinical trial(s). In trials reporting demographic data (n=17), the age of patients ranged from 1-34 years [10-23, 25-27], and the overall male-to-female ratio was 1.7:1 [9-14, 16, 18-27]. The underlying tumor types were heterogeneous; among the included studies, five focused on leukemia (alemtuzumab, imatinib, dasatinib, sorafenib) [10, 11, 14, 19, 27], ten investigated central nervous system tumors (imatinib, erlotinib, cabozantinib, pazopanib, everolimus, temsirolimus) [9, 12, 15-18, 21, 23, 25, 26], and nine investigated other solid tumors (Table I) [10, 13-16, 18, 20, 22, 26]. Most of the pediatric studies included in our analysis were of the phase I and phase II study design; only one was a phase III trial.

Skin rash

The data from all studies reporting all-grade rash were pooled (n=18), and we observed that 127/660 (19%) of patients had experienced rash during treatment. The occurrence of rash ranged from 1.7-86.7% among 18/19 trials (with 10/11 targeted agents) included in the study. A phase II trial of imatinib for refractory/relapsed solid tumors reported the lowest number of patients experiencing a rash (1/59, 1.7%) [22], while a phase I/II trial of vandetanib for medullary thyroid cancer observed the highest proportion (13/15, 86.7%) [13]. Interestingly, when the data from patients treated with EGFR inhibitors (erlotinib, vandetanib) were combined, rash was noted in 42/57 (73.7%) patients. An "acneiform rash" was noted in 14/67 (20.9%) patients in four trials investigating dasatinib (1/11), vandetanib

(3/15), everolimus (7/28), and erlotinib (3/13) [10, 13, 17, 24]; in one report acne was specifically reported (3/28 patients) [17]. In a trial of bevacizumab, one event was noted at the 10mg dosing, and two events were noted at the 15mg dosing [28]. Rash was also noted in 2/39 (5%) of the patients who received a placebo, as part of a randomized controlled trial (RCT) [25]. The terms “dermatitis”, “acneiform”, “macular”, “papular rash”, “maculopapular”, and “rash” had been used interchangeably, and therefore, we grouped them as “rash” in the overall analysis.

Xerosis (dry skin)

In five trials involving imatinib [9], erlotinib [12, 24], vandetanib [13], and cabozantinib [15], all-grade xerosis was noted but the trial involving vandetanib did not provide the exact numbers. Among the remainder four trials reporting data on xerosis, 18/100 (18%) experienced xerosis— among these, 15/18 patients (83.3%) had received erlotinib (EGFR inhibitor).

Mucositis

All-grade mucositis was experienced by 68/402 patients (17%; range, 1.5-85.7%) across 9 trials of rituximab [20], imatinib [9], dasatinib [10], erlotinib [24], cabozantinib [15], everolimus [17, 25], and temsirolimus [18, 23] reporting it. In a trial of bevacizumab, two events were noted at the 15mg dosing [28]. The clinical trial involving extended administration of everolimus for the treatment of subependymal giant cell astrocytoma (SEGA), reported a high proportion of patients (24/28, 85.7%) experiencing stomatitis/mucositis [17]; while a RCT investigating everolimus for the same indication observed mucositis in 24/78 patients (31%), as compared to 8/39 patients (21%) receiving a placebo [25]. Overall, 60/177 patients (33.8%) on a mTOR inhibitor developed mucositis, which contrasts starkly with patients on all other drugs (range, 1.5-15.4%). In the analysis, we grouped studies that clearly reported “mucositis” and/or “stomatitis”, and did not include reports of “mouth ulceration” (noted in 34/216 patients (15.7%) mostly due to everolimus (85.3%) [11, 17, 24, 25]) and aphthous ulcers.

Pruritus

Data on all-grade pruritus were reported in five clinical trials during treatment with imatinib [9, 26], dasatinib [11], and erlotinib [12, 24]. Overall, pruritus was noted in 12/169 patients (7%), with 3/127 patients (2.3%) on Bcr-abl inhibitors experiencing it as opposed to 9/42 of the patients (21.4%) on an EGFR inhibitor.

Other Dermatologic Adverse Events

Pigmentary abnormalities of the skin and/or hair were reported in 9/72 patients (13%) receiving imatinib, dasatinib and cabozantinib [10, 15, 26]. Hair disorders were noted in 9/65 patients (14%), and included trichomegaly (5/29, 17%), hypertrichosis (2/29, 7%), and alopecia (1/29, 3%), reported in a single trial of erlotinib [12], and madarosis (i.e. eyebrow/eyelash loss; 1/36, 3%) with imatinib [26]. Less frequently reported AEs in patients included erythema (15/42, 36%) [12, 24], urticaria (17/252, 7%) [11, 14, 20], acne (4/28, 14%) [17], purpura (1/13, 8%) [24], skin fissures (1/13, 8%) [24], PPE (HFS/HFSR) (6/83, 7%) [14,

15], other “unknown skin changes” (11/169, 7%) [9, 20], exanthem (1/36, 3%) [26], infection (1/29, 3%) [12], and cutaneous eruption (1/36, 3%) [26]. Other miscellaneous dermatologic AEs reported (without clear data) included flushing [10, 13], telangiectasia [13], and photosensitivity [13]. The clinical details regarding “erythema”, “skin fissures”, and “unknown skin changes” were not available.

DISCUSSION

The objective of our study was to provide an overall assessment of dermatologic AEs in pediatric patients treated with targeted anticancer agents. Our results suggest that the incidence and clinical presentation of dermatologic AEs in children mirrors that of adults and product labeling. We noted that a majority of the studies included in our analysis reported rash, but the frequency varied across individual trials/targeted agent(s); the other noteworthy AEs included xerosis, mucositis, and pruritus.

Our findings are consistent with the fact that rash is the most common dermatologic AE encountered during treatment with targeted anticancer therapies [29], and it usually appears in a dose-dependent fashion, varies by tumor type, and may be dose-limiting [10]. Virtually all approved inhibitors of various oncogenic pathways and/or oncoproteins have been associated with the development of rash, although patients on EGFR inhibitors (erlotinib, vandetanib) appeared to be the highest affected (42/57; 73.7%) in our sample. However, the typical “acneiform” morphology was noted in 21.4% (6/28 patients) due to these drugs; this low incidence may be due to inconsistencies in reporting. Besides overexpression by many tumors, EGFR is also constitutively expressed in the skin (epidermis, sebaceous glands, hair follicle) [30], and studies have revealed that its coincidental blockade can lead to disruption of the hair follicle and epidermal differentiation, resulting in follicular obstruction and increased production of pro-inflammatory cytokines (IL-1, TNF- α , chemokines [CCL18, XCL1, CXCL9, and CX3CL1]) [31]. Clinically, this may manifest as folliculitis and rash, the morphology of which is usually acneiform (in adults) [3]. Moreover, the incidence and severity of acneiform rash has been correlated with a better progression-free survival and overall survival in adults, which may serve as a surrogate clinical marker of response to treatment [32, 33]. The rash with mTOR inhibitors is usually a macular and/or papular/acneiform/papulopustular exanthem (Figure 2), and is thought to be due to the inhibition of PI3K-Akt-mTOR signaling, which is one of the downstream effector pathways of the EGFR [34]. A similar macular and/or papular rash has been described with Bcr-abl inhibitors (imatinib, dasatinib; tends to be more follicular and pruritic, i.e., keratosis pilaris-like, Figure 3) [35], which is suggestive of a disturbance in keratinization. It is not known whether these drugs lead to impairment in the formation of filaggrin (implicated in keratosis pilaris, ichthyosis vulgaris) or other epidermal proteins essential for cutaneous homeostasis. Whereas VEGFR inhibitors (cabozantinib, sorafenib, sunitinib, axitinib, pazopanib) result in a macular and/or papular (hypersensitivity-type) rash [3], but the underlying mechanisms have not been identified.

We also observed that a majority of patients in whom xerosis was reported had received treatment with erlotinib (an EGFR inhibitor). Similar to adult patients on these agents, xerosis is characterized by dry and scaly skin reminiscent of atopic dermatitis, and is thought

to be due to loss of water retaining function of the epidermis, developing as a result of disturbed keratinization and sebaceous gland function in skin [36]. While pruritus can be a stand-alone AE, it is well-established that both rash and xerosis, besides other factors (e.g., underlying cancer and age), can be accompanied by pruritus; these details and causality, however, were not specified in the publications included in our analysis. EGFR inhibitor-related pruritus could be attributed to the accumulation of mast cells in dermal adnexal structures of lesional skin [37]. The continued release of inflammatory cytokines in the lesions, followed by the accumulation of mast cells, and subsequent release of mediators (e.g., histamine, TNF- α) upon binding of substance P to the mast cell NK-1 receptor, may stimulate the nociceptive nerve endings in skin leading to the development of pruritus [38]. The benefit of aprepitant (NK-1 receptor antagonist) in erlotinib-induced pruritus further corroborates this [39], although its use must be undertaken with caution given the potential for pharmacokinetic interactions.

Mucositis was reported among patients on inhibitors of different pathways, however, it was highest among patients receiving mTOR inhibitors. Clinically, mTOR-inhibitor associated stomatitis [mIAS], a term preferred over “mucositis” [40], closely resembles aphthous stomatitis. Although the exact mechanisms are not known, the contribution of neutropenia [41] and/or immunosuppression, and mTOR-inhibition-induced impaired angiogenesis (from $\downarrow$ VEGF) [42] and its metabolic effects (e.g., hyperglycemia) [43] leading to impairment of wound healing, cannot be excluded. Topical high-potency corticosteroid creams applied to these lesions have shown benefit in the uncontrolled setting [44].

Other less frequent and noteworthy AEs included hair disorders (e.g., trichomegaly), skin/hair hypo-/depigmentation, and PPE (HFS/HFSR). Trichomegaly (i.e. elongation of eyelashes) was reported in 17% patients across all studies, and is a class-effect of EGFR inhibitors, which may be caused by dysregulation of the keratin gene expression, leading to terminal differentiation of the trichoepithelial cells and an arrest of anagen-catagen transformation in the hair cycle [45]. The dyspigmentation of skin/hair (noted in 13% of the patients) may be due to the inhibition of crucial modulators of pigmentation, namely, c-KIT and its ligand stem cell factor (SCF) [46]. PPE is a painful condition of hands and feet, commonly occurring during pharmacologic inhibition of the VEGF pathway and its receptors (e.g., VEGFR, PDGFR), and may be explained by the perturbed repair mechanisms of endothelial cells and fibroblasts in pressure/friction sites (palms and soles) [47, 48]. The low number of patients (7%) with PPE (HFS/HFSR) across a few pediatric studies in our analysis may not be an accurate reflection of this AE, which has a high incidence in adults receiving VEGFR/PDGFR inhibitors, especially sorafenib.

Only two targeted anticancer agents have been approved (imatinib for Ph+ CML/ALL; everolimus for tuberous sclerosis complex with SEGA) by regulatory agencies for use in children, and an overwhelming majority are in the experimental phase (Figure 4); on the contrary, over 37 targeted anticancer agents are currently approved for use in adults. Proposed explanations for this scenario include a lower incidence of childhood cancer and consequently a mismatch between the choice of a clinical trial and the intended population (leading to inadequate pediatric evaluation of highly efficacious targeted agents), higher expectations vis-à-vis current first-line strategies and the higher costs of treatment [1].

Nevertheless, it can be anticipated that more agents will find their way into pediatric trials and/or cancer care, which underscores the urgent need for familiarity with the accompanying AEs.

Our study provides early notice of the dermatologic AEs that can be anticipated with use of targeted anticancer agents, and emphasizes the need to learn from accumulated clinical insights, AE management strategies, and oversight experiences gained in adult cancer patients (Table II). One must take cognizance of the targeted agent classes, the individual drugs, and their hallmark AEs (on-target, off-target), to ensure consistent dosing of anticancer therapy and improve quality of healthcare. Our findings also offer the opportunity to streamline the quality of AE reporting and realign the focus, to include conditions affecting quality of life in survivors, because major ongoing pediatric trials are yet to report their results (Figure 4).

Our study has some limitations which deserve mention. It was not possible to conduct statistical calculations because of the low number of monotherapy clinical trials, small sample sizes and inconsistent reporting (including terminology) of dermatologic AEs. Therefore, we included phase I/II trials in the analysis, which would preclude meaningful interpretation of any dose-response relationship between targeted agent use and the resulting AEs. Inherent problems pertaining to clinical trials, for example, reporting of AEs only above a certain threshold (%), reporting by the treatment course or number of events, lack of subject-level data, and incomplete details on common terminology criteria for adverse events (CTCAE) versions/grades were noted. As highlighted earlier [49], we also noted that the terminology used to describe rash and oral mucosal complications was not uniform (see: Results section). Lastly, familiarity of pediatric oncologists with the recognition, grading and/or reporting of dermatologic AEs may not be consistent across different institutions.

Targeted anticancer therapies have entered the realm of pediatric cancer care. Hence, there is an urgent need for pediatric health care providers to familiarize themselves with the knowledge to correctly anticipate, appropriately recognize, and effectively manage the accompanying/emerging dermatologic AEs. This is critical because the effect of these novel agents on developmental pathways (sometimes shared by oncogenic pathways) in tissues and organs of growing children are not known. In fact, the slow pace of incorporation of these agents could actually be exploited to rigorously study and systematically report the associated AEs, and design sound AE management strategies and educational programs. The benefits of personalized pre-therapy counseling strategies and early inclusion of a dermatologist in the patient care team cannot be stressed enough. These measures are crucial for favorable clinical outcomes, as dermatologic AEs bear the potential to effect dose alterations of life-saving anticancer therapy, besides resulting in significant morbidity and deterioration in patients' quality of life.

Abbreviations

AE	adverse events
PPE	palmar-plantar erythrodysesthesia

HFS	hand-foot syndrome
HFSR	hand-foot skin reaction
VEGF	vascular endothelial growth factor
EGFR	epidermal growth factor receptor
VEGFR	vascular endothelial growth factor receptor
PDGFR	platelet-derived growth factor receptor
mTOR	mechanistic target of rapamycin
RCT	randomized controlled trial
SEGA	subependymal giant cell astrocytoma
mIAS	mTOR inhibitor associated stomatitis
SCF	stem cell factor
CTCAE	common terminology criteria for adverse events

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Figure 1.
Selection process for studies included in the analysis.

Figure 2. Multiple, discrete, erythematous macular and papular lesions on the trunk (A) and lower abdomen (B) of a 17-year-old male, treated with everolimus for cerebral glioma since 2 years with dramatic improvement. (Images courtesy of Dr Franck Boralevi, Unité de Dermatologie Pédiatrique, Hôpital Pellegrin-enfants, Place Amélie Raba-Léon, 33076 Bordeaux Cedex, France)

Figure 3.

Widespread keratosis pilaris-like rash in a 14-year-old child with chronic myeloid leukemia, 2 weeks after starting treatment with nilotinib. Note the eyebrow involvement with madarosis (A) and keratotic follicular papules with perifollicular erythema on the arm (B); patient also reported pruritus. (Images courtesy of Dr Franck Boralevi, Unité de Dermatologie Pédiatrique, Hôpital Pellegrin-enfants, Place Amélie Raba-Léon, 33076 Bordeaux Cedex, France)

Figure 4. Ongoing clinical trials of targeted anticancer therapies in pediatric patients. For brevity, only drugs being investigated in more than 10 clinical trials are depicted. (Source: Clinicaltrials.gov, accessed July 2014)

Table 1
Characteristics of pediatric studies included in the analysis (n=19), and the major dermatologic adverse events (rash, xerosis, pruritus, mucositis)

Molecular Target	Targeted agent	Author, Year	Enrollment no.	Dosage, Tumor type, Patients treated, n	Median age (range)/ Males (M), Females (F)	Phase of trial	All-grade Rash no./n (%) ^I	All-grade Xerosis no./n (%) ^I	All-grade Pruritus no./n (%) ^I	All-grade Mucositis no./n (%) ^{I,2}
CD52	ALEMTUZUMAB	Angiolillo et al, 2009	13	0.06-0.6mg/kg, ALL, n = 13	8 years (3-20)/ M=8, F=5	2	2/9 (22.22%) ³	n/a	n/a	n/a
CD20	RITUXIMAB	Meinhardt et al, 2010	136	375mg/m ² on day1, CD20+ B-NHL, n = 136	10.4 years (1.5-17.5)/ M=108, F=28	2	n/a	n/a	n/a	2/136 (1.5%)
VEGF-A	BEVACIZUMAB ⁴	Glade Bender et al, 2008	21	5-15mg/kg, Solid tumors (various), n = 19	13 years (1-21) M=10, F=10	1	n/a; 1 event at 10mg, 2 events at 15mg	n/a	n/a	n/a, 2 events at 15mg
Bcr-Abl	IMATINIB	Baruchel et al, 2009	19	440mg/m ² /day, CNS tumors (various), n = 19	9 years (2-18)/ M=12, F=7	2	3/18 (16.7%)	n/a	n/a	n/a
		Bond et al, 2008	70	440mg/m ² /day, Solid tumors, n = 59	16 years (3-29)/ M=48, F=22	2	1/59 (1.7%)	n/a	n/a	n/a
		Boyett et al, 2010	85 (All strata)	350mg/m ² /day, Glioma, n = 33 (Stratum IIA) ⁵	Mean = 10.9 years (SD± 5.4)/ M=13, F=20 (imatinib arm)	1/2	8/33 (24.2%)	0/33 (0%)	0/33 (0%)	2/33 (6.06%) ⁶
		Georger et al, 2009	36	340 - 440mg/m ² /day, Solid tumors (incl. CNS tumors), n = 36	13.7 years (2.2-22.5)/ M=21, F=15	0 (exploratory)	1/36 (2.8%)	n/a	1/36 (2.8%)	n/a
		Lakshmaiah et al, 2012	43	260mg/m ² , CML, n = 43	15 years (7-20)/ M=24, F=19	Retrospective study	8/43 (18.6%)	n/a	n/a	n/a
	DASATINIB	Aplenc et al, 2011	39	50-110mg/m ² /dose, Solid tumors (various), n = 28 Ph. chr.+ve leukemia, n = 11	11 years (2-20)/ M=20, F=19	1	7/18 (38.8%) ^{7,8}	n/a	n/a	1/18 (5.5%)
							5/11 (45.5%) ⁹	n/a	n/a	n/a
EGFR	ERLOTINIB	Zwaan et al, 2013	58	60 to 120mg/m ² , Leukemias, n = 58	10 years (n/a)/ M=39, F=19	1	9/58 (15.5%)	n/a	2/58 (3.4%)	n/a
		Astellas Pharma Inc., 2013	25 (Arms 1,2)	85mg/m ² /day, Ependymoma, erlotinib, n= 13 vs. etoposide, n = 12	Mean = 12.8 (SD=5.87)/ M=10, F=3 (erlotinib arm)	2	10/13 (76.9%) ¹⁰	1/13 (7.7%)	3/13 (23.1%)	2/13 (15.4%) ⁶
		Georger et al, 2011	51 (Groups 1,2)	75-150mg/m ² /day, Brainstem Glioma & Brain Tumors; Group 1, n = 29 ¹¹	10 years (4-20)/ M=15, F=14	1	19/29 (65.5%) ^{12,13}	14/29 (48.2%)	6/29 (20.7%) ¹³	n/a
EGFR/VEGFR	VANDETANIB	Fox et al, 2013	16	100-150mg/m ² /day, MTC (MEN2B associated), n = 16	14 years (9-17)/ M=8, F=8	1/2	13/15 (86.7 %) ¹⁴	n/a	n/a	n/a

Molecular Target	Targeted agent	Author, Year	Enrollment no.	Dosage, Tumor type, Patients treated, n	Median age (range)/ Males (M), Females (F)	Phase of trial	All-grade Rash no./n (%) ¹	All-grade Xerosis no./n (%) ¹	All-grade Pruritus no./n (%) ¹	All-grade Mucositis no./n (%) ^{1,2}
VEGFR	SORAFENIB	Widemann et al, 2012	65	150-325mg/m ² /dose, Leukemia and solid tumors, n = 60	14 years (4-21)/ M=37, F=23	1	3/58 (5.1%) ^{1,5}	n/a	n/a	n/a
	CABOZANTINIB	Chuk et al, 2014	30	30-55mg/kg/day, Solid tumors (various including CNS), n = 25	14 years (4-18)/ M=n/a, F=n/a	1	5/25 (20%)	3/25 (12%)	n/a	1/25 (4%)
	PAZOPANIB	Glade Bender et al, 2013	53	275-600mg/m ² , Soft tissue sarcoma and solid tumors (various including CNS tumors), n = 51	12.9 years (3.8-23.9)/ M=26, F=25	1	4/48 (18%) ^{1,5,16}	n/a	n/a	n/a
mTOR	EVEROLIMUS	Franz et al, 2013	117 (Arms 1,2)	4.5mg/m ² /day, Astrocytoma (TSC associated), n = 117 (placebo, n = 39)	9.5 years (1-23.9)/ M=49, F=29 (everolimus arm)	3 RCT	9/78 (12%) placebo, 2/39 (5%)	n/a	n/a	24/78 (31%); placebo, 8/39 (21%) ²
		Krueger et al, 2013	28	2.1-12.3mg/m ² , Astrocytoma, n = 28	11 years (3-34)/ M=n/a, F=n/a	1/2	7/28 (25%) ^{17,18}	n/a	n/a	24/28 (85.7%) ^{2,19}
	TEMSIROLIMUS	Georger et al, 2012	52	75mg/m ² , Glioma, neuroblastoma, and rhabdomyosarcoma, n = 52	8 years (1-21)/ M=35, F=17	2	7/52 (13%)	n/a	n/a	6/52 (12%)
		Spunt et al, 2011	19	10-150mg/m ² , Solid tumors including brain tumors, n=19	11 years (4-21)/ M=11, F=8	1	6/19 (32%)	n/a	n/a	6/19 (32%)

Abbreviations: CNS = central nervous system; MTC = medullary thyroid cancer; RCT = randomized controlled trial; SD = standard deviation; TSC = tuberous sclerosis complex

¹ Adverse events noted among evaluable patients;

² All instances of stomatitis were also included;

³ Only the data from treatment course #1 was included;

⁴ Not included in the analysis;

⁵ Only stratum IIA administered imatinib in monotherapy (Strata I & IIB data were not included);

⁶ Reported as either “stomatitis/pharyngitis” or “stomatitis”;

⁷ Patient 31 had a dose limiting toxicity, resulting in a desquamating grade 3 rash at 110 mg/m² on course 3 and course 9;

⁸ The denominator is the number of patients evaluable for toxicity;

⁹ Toxicity was noted during course 1 at 85mg/m²;

¹⁰ Reported as rash, acneiform dermatitis, maculo-papular rash, macular rash, papular rash;

¹¹ Group 1 was treated with erlotinib; Group 2 was treated with erlotinib and radiotherapy;

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¹² Reported as “acne/rash/folliculitis”;

¹³ Group 1 data only i.e. erlotinib recipients;

¹⁴ Reported rash of grades 1 & 2 during cycles 1 and 2;

¹⁵ Cycle 1 data included only; for rest of the 23 cycles, the data was reported in a mixed manner - for e.g. rash/hand foot; the trial used a tablet and suspension version; only the solid tumor stratum had rash;

¹⁶ Reported as rash maculopapular/hand-foot;

¹⁷ Core-extension phase data;

¹⁸ Reported as acneiform dermatitis;

¹⁹ Reported as “stomatitis” and “mouth ulceration” separately

Table II
Summary of the most common dermatologic AEs from inhibition of key molecules and molecular pathways

◆EGFR: MEK	◆ VEGF	◆ VEGFR	◆ Bcr-Abl	◆ CTLA-4	◆ BRAF	◆ mTOR
SKIN CHANGES						
(+++)		(++) Macular ± papular rash ¹	(+) Macular ± papular rash ¹	(+) Macular ± papular rash ¹	(++) Macular ± papular rash ¹	(+) Macular ± papular rash ¹
(+++)		(+) Acneiform/Papulopustular rash ²				(+) Acneiform/Papulopustular rash ²
			(+) Keratosis pilaris-like rash (N.D)		(++) Keratosis pilaris-like rash	
(+++)		(++) Xerosis ³	(++) Xerosis ³		(++) Xerosis ³	(+) Xerosis ³
(++)		(++) Pruritus ⁴	(++) Pruritus ⁴	(++) Pruritus ⁴	(+) Pruritus ⁴	(+) Pruritus ⁴
(++)						
(++)						
(++)						
	(+) HFS/PPE ⁷	(++) HFS/PPE ⁷			(+) HFS/PPE ⁷	
(+) Photosensitivity ⁸ (V)		(+) Photosensitivity ⁸	(+) Photosensitivity ⁸		(++) Photosensitivity ⁸	
(+) Hyperpigmentation	(+) Hyperpigmentation (A)		(+) Hyperpigmentation (I)			
		(+) Hypopigmentation	(+) Hypopigmentation (I)			
			(+) Depigmentation ⁹ (I)	(++) Depigmentation ⁹		
(+) Impaired wound healing ¹⁰	(++) Impaired wound healing ¹⁰					(++) Impaired wound healing ¹⁰
		(+) Verrucous lesions/Cutaneous Neoplasms ¹¹ (So)			(++) Verrucous lesions/Cutaneous Neoplasms ¹¹	
HAIR CHANGES						
(++) Alopecia ¹²	(+) Alopecia ¹²	(++) Alopecia ¹²	(+) Alopecia ¹²	(+) Alopecia ¹²	(++) Alopecia ¹²	(+) Alopecia ¹²
(++) Hypertrichosis ¹³ ,						

◆EGFR; MEK	◆ VEGF	◆ VEGFR	◆ Bcr-Abl	◆ CTLA-4	◆ BRAF	◆ mTOR
(++) Trichomegaly ¹⁴						
(++) Curling ¹⁵		(++) Curling ¹⁵			(++) Curling ¹⁵	
(+) Hyperpigmentation ¹⁶						
		(+) Hypopigmentation ¹⁷ (C)	(+) Hypopigmentation ¹⁷			
NAIL CHANGES						
(++) Nail plate abnormalities		(+) Nail plate abnormalities				(+) Nail plate abnormalities
(++) Paronychia ¹⁸		(+) Paronychia ¹⁸				(+) Paronychia ¹⁸
	(+) Splinter hemorrhages ¹⁹ (B)					
MUCOSAL CHANGES						
(+) Mucositis ²⁰ , Mouth ulcers	(+) Mucositis ²⁰ , Mouth ulcers	(+) Mucositis ²⁰ , Mouth ulcers	(+) Mucositis ²⁰ , Mouth ulcers			(++) Mucositis ²⁰ , Mouth ulcers

a)* indicates therapeutic drug target(s); b) **Incidence:** + <10%, ++ 10-30%, +++ >30%; c) **KA/cuSCC:** keratoacanthoma/cutaneous squamous cell carcinoma; d) **Epidermal growth factor receptor (EGFR) inhibitors:** cetuximab (Erbix[®]), erlotinib (Tarceva[®]), panitumumab (Vectibix[®]), gefitinib (Tykerb[®]), lapatinib (Tykerb[®]), pertuzumab (Perjeta[®]), afatinib (Afinitor[®]); **EGFR/vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitors:** vandetanib (V) (Caprelsa[®]), regorafenib (Stivarga[®]), cabozantinib (C) (Cometriq[®]); **Bcr-Abl tyrosine kinase inhibitors:** imatinib (I) (Gleevec[®]), nilotinib (N) (Tasigna[®]), dasatinib (Sprycel[®]), ponatinib (Iclusig[®]); **cytotoxic T-lymphocyte-associated protein (CTLA)-4 inhibitor:** ipilimumab (Yervoy[®]); **BRAF inhibitors:** vemurafenib (Zelboraf[®]), dabrafenib (Tafinlar[®]); **mTOR (mechanistic target of rapamycin) inhibitors:** everolimus (Afinitor[®]), temsirolimus (Torisel[®]); e)

¹These are often reported as “maculopapular” in literature,

²Rash is of ‘acneiform’ morphology,

³Implies dry and scaly skin,

⁴Can be generalized or localized to the skin lesions/eruption/xerosis,

⁵Occur commonly on the tips of fingers and toes,

⁶These may be bacterial, viral or superficial fungal infections of the skin and/or its appendages,

⁷Also known as hand-foot syndrome/hand-foot skin reaction,

⁸Manifests as an erythematous rash on sun-exposed areas,

⁹Clinically, this is vitiligo-like,

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- ¹⁰ Post-operative wound healing is impaired,
- ¹¹ These are primarily KAs/ cuSCCs,
- ¹² Hair loss is mainly seen on the scalp but other areas (body, pubis) can also be involved,
- ¹³ Excessive hair growth,
- ¹⁴ Elongation of eyelashes,
- ¹⁵ May affect the scalp hair and/or eyelashes,
- ¹⁶ Darkening or re-pigmentation of hair,
- ¹⁷ Lightening of hair,
- ¹⁸ Inflammation and/or infection of the lateral nail folds; fungal infection of the nails may rarely occur,
- ¹⁹ Small areas of bleeding which appear as straight lines under the nail plate,
- ²⁰ Reported interchangeably in literature as stomatitis