Economic Burden of Dermatologic Adverse Events Induced by Molecularly Targeted Cancer Agents

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Objective: To report the financial impact of diagnosing and treating the dermatologic toxicities (dTs) that develop in patients receiving targeted anticancer therapies.

Design: Single-center retrospective and prospective medical record data extraction.

Setting: Department of Dermatology, Northwestern University, Chicago, Illinois.

Patients: One hundred thirty-two adults who presented between November 1, 2005, and June 30, 2008, and who were diagnosed as having 1 primary cancer type and were treated with 1 molecularly targeted agent.

Main Outcome Measure: Standard billable costs to the patient for dT-related medications, clinic visits, laboratory and diagnostic testing, and therapeutic procedures.

Results: The 132 patients had a median of 3 clinic visits for dT management with a median cost of $1920 per patient. Sorafenib was associated with the most costly overall median cost per patient ($2509 per patient), and imatinib was associated with the least costly overall median cost per patient ($1263 per patient). Among the 7 targeted drugs and all 10 dTs, the most costly dT (measured by cost of treatment with medications) was hand/foot skin reaction, associated with sorafenib therapy (median cost, $968 per patient) (P < .001). The second most costly dT was panitumumab-associated acneiform eruption (median cost, $933 per patient) (P < .001).

Conclusion: The cost of diagnosis and treatment of dTs associated with targeted agents contributes to the overall economic burden of cancer care. Efforts toward the prevention of dTs may be important for decreasing the financial burden in oncology.

Arch Dermatol. 2011;147(12):1403-1409

TARGETED AGENTS THAT INHIBIT TUMORS FROM GROWING AND METASTASIZING affect the function of cells in the skin and appendages because the epidermal growth factor receptor (EGFR) is also expressed by basal keratinocytes, sebocytes, the outer layer of the hair follicle, and some endothelial cells, thus leading to dermatologic toxicities (dTs). These toxic effects are the most common adverse effects of EGFR inhibitor therapy and occur in more than 90% of patients. They include papulopustular eruption/acneiform eruption (45%-100% of patients), alopecia (14%-21%), erythema (12%-18%), periungual inflammation (12%-16%), nail changes (10%-29%), hair modifications (9%), pruritus (8%-35%), xerosis (7%-35%), and skin hyperpigmentation. Similar dTs, such as hand/foot skin reaction (HFSR), seborrheic dermatitis–like rash, scalp dysthesia, xerosis, and mucositis, are seen with sorafenib, sunitinib, and other inhibitors of the vascular endothelial growth factor receptor, but the spectrum of cutaneous adverse effects is less pronounced than with EGFR inhibitors.

Dermatologic toxicities are noteworthy because of their relatively high frequency, effect on patient quality of life (QOL), effect on adherence, increased risk of infections, and effect on cancer therapy dosing. Management of such adverse effects is paramount to maintain dose intensity and QOL. This study seeks to evaluate selected tangible resource costs associated with the diagnosis and treatment of dTs induced by 7 molecularly targeted agents.

METHODS

This study was approved by the Northwestern University institutional review board. Participants were patients who presented to the SERIES (Skin and Eye Reactions to Inhibitors of EGFR and Kinases) Clinic.

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A referral clinic for DTs of cancer therapies. All the patients were seen by the same dermatologist (M.E.L.) after the onset of cutaneous toxic reactions. They were treated per standard of care with appropriate workup and treatment, depending on the severity and type of DT present. The medical records of 132 patients were reviewed to evaluate the costs of DT management.

All the patients were diagnosed as having 1 primary cancer type (Table 1) and were treated with 1 molecularly targeted agent (Table 2). Cancer types having less than 5 patients were grouped into the “other” category. For this study, all costs are standard billable costs to the patient as obtained from the Medicare Physician Fee Schedule for outpatient services in effect at the time of the study. Costs for DT-related medications, clinic visits, laboratory and diagnostic testing, and therapeutic procedures were recorded. Laboratory and diagnostic testing included blood testing (ie, complete blood cell count with differential cell count), culture and sensitivity (ie, wound), biopsy, and imaging (ie, magnetic resonance imaging of finger). Medication costs for management of DTs were determined using the average wholesale price in the Red Book 2008 and a 1.4 multiplier to reflect billable costs to patients.

Management of DTs varied on a case-by-case basis. Topical medications (in a cream, lotion, ointment, gel, shampoo, or therapeutic tape formulation) included antibacterial, anti-inflammatory, antipruritic, anesthetic, retinoid, keratolytic, moisturizing, and hair growth–stimulating agents. Oral medications included antibacterial, anti-inflammatory, antipruritic, retinoid, and pain-alleviating agents. Therapeutic procedures included lesion destruction (ie, cryotherapy), nail plate avulsion, nail debridement, and incision and drainage of abscess.

Information collected from medical records included age, sex, race (when available), Fitzpatrick skin type (I-VI), cancer type, and other relevant demographic information. The data were analyzed using statistical software (SPSS, version 20, IBM, Armonk, NY). The significance level was set at .05.

### Table 1. Patient Characteristics by Primary Cancer Type

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Colorectal</th>
<th>Lung</th>
<th>Breast</th>
<th>Renal</th>
<th>Head and Neck</th>
<th>Pancreatic</th>
<th>Other</th>
<th>All Cancers</th>
<th>P Value</th>
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<td>13 (10)</td>
<td>12 (9)</td>
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<td>3 (25)</td>
<td>1 (14)</td>
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<td>79 (60)</td>
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<td>0</td>
<td>0</td>
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<td>Skin type, No. (%)</td>
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<td>6 (46)</td>
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<td>4 (57)</td>
<td>3 (60)</td>
<td>6 (33)</td>
<td>54 (41)</td>
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<td>1 (14)</td>
<td>2 (40)</td>
<td>7 (39)</td>
<td>39 (30)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

a Other includes brain cancer, gastrointestinal stromal tumor, leukemia/lymphoma, ovarian cancer, hepatic cancer, angiosarcoma, Ewing sarcoma, hemocytoma, and gastroesophageal cancer.

b Data unavailable for 1 patient.

### Table 2. Patient Characteristics by Targeted Drug

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Erlotinib</th>
<th>Cetuximab</th>
<th>Sorafenib</th>
<th>Lapatinib</th>
<th>Panitumumab</th>
<th>Sunitinib</th>
<th>Imatinib</th>
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<td>6 (40)</td>
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<td>6 (86)</td>
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<td>Skin type, No. (%)</td>
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<td>4 (57)</td>
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<td>39 (30)</td>
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</tbody>
</table>

a Data do not sum to the total number of the population due to unavailability.

b Data unavailable for 1 patient.
type, targeted drug, total number of visits to the SERIES clinic in the study time frame, type of dT, and dT severity grade (0-3) (National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0).25

STATISTICAL ANALYSIS

Descriptive statistics include counts and percentages, medians, interquartile ranges (25th-75th percentiles), and ranges. Owing to the skewed nature of cost to treat, analyses of cost data are based on medians (Kruskal-Wallis or Friedman tests). In addition, medians reflect what might be a typical cost per individual because it is less sensitive to outliers (ie, from individuals who had no dT [and no cost] or from individual treatments incurring unusually high costs). In instances in which sample sizes prohibited testing, medians are presented without further formal testing. Additional analyses of independent data, including count data, are based on χ² tests or Fisher exact tests, depending on sample size restrictions. Moreover, related count data (such as dT events by drug) were analyzed using the Cochran Q test.

RESULTS

A total of 132 patients were evaluated (Tables 1 and 2). The median cost for dT diagnosis and treatment was $1920 per patient (range = $21-$10,912), with a median cost per visit of $674 (range = $21-$8,451) (Table 3). The median costs by category of treatment were as follows: medications ($844), clinic visits ($796), laboratory and diagnostic testing ($435), and therapeutic procedures ($316). The Figure depicts these costs as related to targeted drug.

FREQUENCY OF dTs AND COSTS OF TREATMENT BY TARGETED DRUG

The frequencies of the following dTs as related to each drug were analyzed: acneiform eruption, pruritus, xerosis, HFSR, alopecia, paronychia and nail changes, seborrheic dermatitis/sebopsoriasis, mucositis/stomatitis/
In patients treated with Erlotinib, the most common dT was acneiform eruption (98%), followed by xerosis (74%) and pruritus (50%). In patients who developed acneiform eruption (n = 41), most were grade 2 (54%). Toxicity grading of acneiform eruption differed significantly among the 7 targeted drugs (P < .03). Grade 3 was the most costly acneiform eruption to treat by grade of severity (median cost = $2305). The median cost and median cost per visit are summarized in Table 3. The following median costs were noted: medications ($813), clinic visits ($650), laboratory and diagnostic testing ($180), and therapeutic procedures ($0) (Figure). A median cost of $0 indicates that only a few patients treated with erlotinib had a therapeutic procedure cost, and this skewed the results to indicate a median cost of $0.

**CETUXIMAB**

In patients treated with cetuximab, the most common adverse effects were acneiform eruption (97%), xerosis (74%), and paronychia and nail changes (41%). Grade 2 was also the most common dT grade (45%) in those with acneiform eruption. The median cost and median cost per visit in patients treated with cetuximab are summarized in Table 3. The following median costs were noted: medications ($823), clinic visits ($760), laboratory and diagnostic testing ($180), and therapeutic procedures ($0) (Figure).

**SORAFENIB**

In patients treated with sorafenib, the most common dT was HFSR (93%), followed by acneiform eruption (80%) and mucositis/stomatitis/cheilitis (33%). Of those who developed HFSR (n = 14), most were grade 3 (43%). The median cost and median cost per visit are summarized in Table 3. Sorafenib was associated with the most costly overall median cost per patient (cost for medications, clinic visits, laboratory and diagnostic testing, and therapeutic procedures) (median, $2509 per patient) (P = .35) and the highest median cost per visit ($828 per patient) (Table 3). The following median costs were noted: medications ($1672), clinic visits ($796), and laboratory and diagnostic testing ($90) (Figure). No patients underwent therapeutic procedures.

**LAPATINIB**

In patients treated with lapatinib (n = 13), the most common adverse effect was acneiform eruption (85%), followed by xerosis (54%) and pruritus (31%). For acneiform eruption (n = 11), most were grade 2 (64%). The median cost and median cost per visit in patients treated with lapatinib are summarized in Table 3. The following median costs were noted: medications ($528), clinic visits ($796), laboratory and diagnostic testing ($523), and therapeutic procedures ($0) (Figure).

**PANITUMUMAB**

In patients treated with panitumumab, the most common dT was acneiform eruption (100%), followed by xerosis (82%) and paronychia and nail changes (45%). With acneiform eruption (n = 11), the most frequent grade was 3 (36%). The median cost and median cost per visit in patients treated with panitumumab are summarized in Table 3. The following median costs were noted: medications ($1072), clinic visits ($796), laboratory and diagnostic testing ($180), and therapeutic procedures ($0) (Figure).

**SUNITINIB**

Patients treated with sunitinib most commonly experienced HFSR (57%), followed by seborrheic dermatitis/sebopsoriasis (43%) and xerosis (29%). Of the 4 patients who developed HFSR, 50% developed grade 2 and 50% developed grade 3. The median cost and median cost per visit are summarized in Table 3. The following median costs were noted: medications ($1091), clinic visits ($796), laboratory and diagnostic testing ($613), and therapeutic procedures ($0) (Figure).

**IMATINIB**

In patients treated with imatinib, the most common adverse effects were acneiform eruption (60%) and pruritus (60%). The median cost and median cost per visit are summarized in Table 3. Imatinib was associated with the least costly overall median cost per patient (cost for medications, clinic visits, laboratory and diagnostic testing, and therapeutic procedures) ($1263 per patient) among all targeted therapies. The following median costs were noted: medications ($700), clinic visits ($528), and laboratory and diagnostic testing ($523). No patients underwent therapeutic procedures (Figure).

**COSTS FOR MEDICATIONS AS RELATED TO TREATMENT OF dTs BY TARGETED DRUG**

The median cost for medications used in the treatment of each dT was compared and analyzed by targeted drug. This analysis includes all patients taking each drug, so comparisons entail the probability of dT, as well as the cost to treat the dT, should it occur. Minimum and median costs of $0 are indicative of patients who did not experience the dT of interest.

A total of 117 patients (89%) developed an acneiform eruption. The median cost for treatment of acneiform eruption with medications was $279 (range = $0-$7553) (P < .001). Acneiform eruption associated with panitumumab had the greatest median cost for medications ($933, range = $30-$2232), whereas sunitinib-associated acneiform eruption had the lowest median cost for medications ($0, range = $0-$651). The median cost of HFSR differed across all targeted drugs (P < .001).
Sorafenib was associated with the most-costly-to-treat HFSR (median cost = $968, range = $0-$3189), and lapatinib combined with capecitabine and imatinib induced HFSR with a median cost of treatment of $50 (range = $0-$479 for lapatinib and range = $0-$208 for imatinib).

Of all dTs associated with EGFR inhibitors (erlotinib, cetuximab, lapatinib, and panitumumab), acneiform eruption represented the greatest median cost for medications ($473, $271, $63, and $933, respectively) (P < .001). Of all dTs associated with imatinib, pruritus had the greatest cost for medications at a median cost of $74, although this was not significant (P = .06). Of all dTs associated with sorafenib and sunitinib, HFSR had the greatest cost for medications at a mean cost of $968 (P < .001) and $619 (P = .03), respectively.

**FREQUENCIES OF dTs AS RELATED TO DRUG GROUP OR CLASS**

When the 7 targeted therapies were grouped as monoclonal antibodies (cetuximab and panitumumab) or tyrosine kinase inhibitors (erlotinib, imatinib, lapatinib, sorafenib, and sunitinib), differences between the 2 groups were noted. The following dTs were more common among monoclonal antibodies than among tyrosine kinase inhibitors: acneiform eruption (P = .008), xerosis (P = .007), and paronychia and nail changes (P = .02). An HFSR was more common among tyrosine kinase inhibitors than among monoclonal antibodies (P < .001).

**COMMENT**

Dermatologic toxic reactions associated with molecularly targeted agents occur frequently (in > 50% of patients) and are characterized by papulopustular eruption/ acneiform eruption, xerosis, pruritus, erythema, paronychia and nail changes, hair modifications, infections, and HFSR. These dTs can negatively impact QOL and may result in EGFR inhibitor dose modification, interruption, or discontinuation. Awareness of these toxic reactions and the economic burden that they pose is of paramount importance, especially because these agents are being tested in adjuvant settings and their use is expanding. Furthermore, preemptive skin treatment with moisturizers, sunscreen, topical corticosteroids, and oral antibiotics may reduce specific grade 2 or greater skin toxic reactions and improve QOL in patients treated with EGFR inhibitors.

The present study found that dTs associated with sorafenib were the most costly to treat, possibly owing to a relatively high incidence of HFSR and the usual need for pain control, an important factor affecting these patients’ QOL. The incidence of HFSR has been reported to be higher with sorafenib (10%-62%) than with sunitinib (10%-28%). This finding was also demonstrated in the analysis in that 93% of patients treated with sorafenib and 57% of patients treated with sunitinib presented with HFSR. In this study, 3 patients treated with lapatinib and 1 treated with imatinib also developed HFSR. This could be explained by concurrent treatment with other agents that are known to induce HFSR, such as capecitabine. Furthermore, HFSR has also been reported in less than 1% of patients undergoing lapatinib monotherapy.

A class effect of toxicities is suggested by the similar spectrum of events observed with monoclonal antibodies and tyrosine kinase inhibitors. The incidence of acneiform eruption has been reported to be higher in patients treated with monoclonal antibodies. The present findings are concordant in that 98% of patients treated with monoclonal antibodies developed acneiform eruption in contrast to 83% of patients treated with the other 5 targeted therapies (P = .008). A seborrhoeic dermatitis–like rash has been reported in patients treated with multikinase inhibitors. We found that 43% of patients (n = 3) treated with sunitinib and 20% of patients (n = 3) treated with sorafenib developed seborrhoeic dermatitis/sebopsoriasis (P = .04). Another example of a class effect with the multikinase inhibitors is HFSR, described previously herein. These class effects should alert physicians to the anticipated adverse effects of a specific targeted drug and provide a rationale for patient education and prophylactic therapies that may mitigate such dTs.

Acneiform eruption is known to commonly occur in patients receiving targeted therapy. The present study found this DT to be present in 89% of patients. The higher frequencies of dTs, such as paronychia and xerosis, in the present study compared with previous studies are likely due to the selected patient population because these patients had been referred to the SERIES dermatology specialty clinic after they developed cutaneous toxic reactions. It is also possible that dTs (especially mild) may have been underreported in previous studies. Furthermore, differences may also be explained by the use of variable dosing of molecularly targeted therapies. We did not include drug dosing as one of the study variables, although a dose-dependent effect on dTs has been well described.

The National Cancer Institute Common Toxicity Criteria for Adverse Events scale has several limitations, including being unable to assess the degree of functional (clinical and psychosocial) impairment secondary to dTs. Furthermore, differences in the definition and grading of dTs make it difficult to compare the incidence and severity of dTs associated with different inhibitors. Other limitations of the study include clinic visits for some of the study patients that occurred outside of the study time frame (before November 1, 2005, or after June 30, 2008) that do not generate study data. In addition, because it is a cross-sectional study, many of the cancer types and treatment drugs have limited sample sizes, which reduced the power if not the possibility of any stringent cost comparisons. Finally, we excluded concurrent medications and therapies in the study analysis, and these may affect the development and severity of dTs.

To our knowledge, this study is the first to report the economic burden of diagnosing and treating dTs that have a significant financial impact in the management of patients with cancer. Increased awareness and early treatment of these toxic reactions are required to decrease health care costs, minimize interruption of therapy, and improve patient QOL and outcome. As cancer therapy
and clinical outcomes improve, patients will be treated for longer periods, and interventions that prophylactically mitigate such toxic reactions are essential to minimizing the economic burden for cancer care.3

Accepted for Publication: June 7, 2011.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Abraham, West, and Lacouture. Acquisition of data: Borovicka, Calahan, Gandhi, Abraham, and Lacouture. Analysis and interpretation of data: Borovicka, Calahan, Kwasny, Haley, and Lacouture. Drafting of the manuscript: Borovicka. Critical revision of the manuscript for important intellectual content: Calahan, Gandhi, Abraham, Kwasny, Haley, West, and Lacouture. Statistical analysis: Kwasny. Administrative, technical, or material support: Borovicka, Calahan, Gandhi, Abraham, Haley, West, and Lacouture. Study supervision: Lacouture.

Financial Disclosure: Dr West serves as a paid consultant to Sage Products Inc and has also served as a consultant or received honoraria from Shionogi Pharma. Dr Lacouture serves as a consultant or receives honoraria from OSI Pharmaceuticals Inc, Bristol-Myers Squibb, ImClone Systems Inc, Eli Lilly & Co, Bayer HealthCare Pharmaceuticals Inc, Onyx Pharmaceuticals Inc, GlaxoSmithKline, Amgen Inc, Pfizer, Vertex Pharmaceuticals, and Vivus. The Department of Dermatology at Northwestern University has received or is currently receiving research grants from Abbott Labs, Skin of Color Society, Medics Pharmaceutical Corp, Yaupon Therapeutics, Biogen, NuGene, Basilea Pharmaceutica, RegeneRx, Johnson & Johnson, Galderma, 3M, Allergan, Lindi Skin, Hana Biosciences, Regeneron, Celgene, American Society for Dermatologic Surgery, IPC Pharma, Astellas, Alwyn, Leo Pharma, National Institutes of Health, Shape Pharmaceuticals, Northgate Technologies Inc, OSI Pharmaceuticals Inc, Centocor Ortho Biotech Inc, Genentech, Bayer, Amgen, Pierre Fabre Pharmaceuticals, GlaxoSmithKline, Bristol-Myers Squibb, Pfizer, Onyx Pharmaceuticals, Novartis, and ImClone Systems Inc.

Funding/Support: This study was supported in part by a Zell Scholarship from the Robert H. Lurie Comprehensive Cancer Center (Dr Lacouture) and by a Dermatology Foundation Career Development Award (Dr Lacouture).

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

Previous Presentations: This study was read in part at the Annual Meeting of the American Academy of Dermatology; March 7, 2010; Miami, Florida; and displayed as a scientific poster at the Annual Meeting of the American Society of Clinical Oncology; June 4-8, 2010; Chicago, Illinois; the Multinational Association of Supportive Care in Cancer 2010 International Symposium; June 24–26, 2010; Vancouver, British Columbia, Canada; and the Ninth International Kidney Cancer Symposium; October 1-2, 2010; Chicago, Illinois.

REFERENCES

Announcement

Tips for Taking Publishable Photographs

In a very visual specialty, great medical photographs can enhance the understanding of any dermatologic manuscript. To ensure that your photographs meet minimal standards for publication in the *Archives of Dermatology*, please keep the following tips in mind.

**Technical considerations:**
- Set your camera to 3 megapixels or greater. If you plan to crop extensively, an even higher resolution is desirable. If using .JPG file type, use the highest quality .JPG setting.¹
- When sending a photograph to a journal, send the original or cropped image file (with .JPG or .TIF extension). *Do not* send an image pasted into a Microsoft Word or Microsoft Powerpoint document.¹

**Legal considerations:**
- Obtain proper written consent to publish the image if there is any identifiable patient information in the picture. If in doubt, obtain consent. Consent forms are available at http://www.archdermatol.com.¹
- Use of black bars over the eyes of a patient is not acceptable to mask the identity of a patient.²

**Quality considerations¹:**
- Use a solid colored background to eliminate background distracters.
- When submitting before and after images, maintain consistency of lighting, background, framing, patient positioning, and elimination of distracters to the extent possible. This lends credibility to the images and makes it easy for readers to focus on the subject of the image.¹
- When you photograph the image, frame the subject to crop out unnecessary distracting features to keep readers focused on the subject.