ABSTRACT

BACKGROUND: There are currently many approved agents for the treatment of metastatic melanoma (MM), the most aggressive form of skin cancer. Treatments may include systemic therapies such as ipilimumab, dacarbazine, temozolomide, high-dose interleukin 2, interferon α, dacarbazine- or temozolomide-based combination chemotherapy/biochemotherapy, paclitaxel, paclitaxel/cisplatin, and paclitaxel/carboplatin, as well as the targeted therapies vemurafenib, dabrafenib, and trametinib for patients with BRAF V600 mutation. However, all treatment options are associated with different adverse events (AEs) and, in some instances, considerable toxicity. The occurrence of such treatment-related AEs can lead to higher health care resource utilization and increasing treatment and patient management costs. An understanding of the economic burden of these AEs will therefore enable better management of health care expenditures, not just for existing therapies, but also for new and novel treatments in development.

OBJECTIVE: To estimate the incremental health care costs of specific AEs among patients with MM treated with paclitaxel, vemurafenib, ipilimumab, dacarbazine, temozolomide, high-dose interleukin 2, or interferon α, along with AEs known to be associated with dabrafenib and trametinib.

METHODS: This cohort study employed a retrospective administrative claims-based analysis of MarketScan commercial and Medicare supplemental databases from July 1, 2004, to April 30, 2012. Patients included those aged ≥18 years who had diagnosed melanoma (ICD-9-CM code 172.xx) with ≥1 diagnosis of metastasis and ≥1 claim for any of the 7 study treatments. Health care encounters for AEs of interest were based on ICD-9-CM diagnosis/procedure codes. Incremental cost per AE was determined by comparing the 30-day expenditures in patients with the event to patients without the event based on a shadow event date. Multivariate generalized linear models (GLMs) with a log-link function and gamma distribution were utilized to control for baseline differences between groups.

RESULTS: A total of 2,621 patients with MM were included. Mean age was 56.0 years (SD ± 13.0); 64% were male; and 24% had a diagnosis of primary or secondary brain cancer at the time of MM diagnosis. GLM-based estimate of 30-day incremental costs by AE category were metabolic, $9,135 (95% CI = $6,404-$12,392); hematologic/lymphatic, $8,450 (95% CI = $6,528-$10,633); cardiovascular, $6,476 (95% CI = $4,667-$8,541); gastrointestinal, $6,338 (95% CI = $4,740-$8,122); skin/subcutaneous, $9,012 (95% CI = $6,999-$11,025); central nervous system/psychiatric, $5,903 (95% CI = $3,842-$8,313); and pain, $5,078 (95% CI = $3,392-$7,012).

CONCLUSIONS: Incremental costs associated with many MM treatment-related AEs are substantial. New approaches to prevent and/or better manage these events may be important factors in decreasing the financial burden of existing and new therapies for metastatic melanoma.

What is already known about this subject

- Metastatic melanoma is the most aggressive form of skin cancer, with a median overall survival of less than 1 year.
- Despite the wide armamentarium of systemic and targeted therapies available for the treatment of metastatic melanoma, all are associated with different adverse event profiles and toxicities, including skin-related toxic effects, fatigue, anemia, peripheral neuropathy, nausea, elevated serum glutamate oxaloacetic transaminase levels, vomiting, and stomatitis, among others.

What this study adds

- This retrospective cohort study is the first to estimate the health care costs of specific treatment-related adverse events among patients with metastatic melanoma receiving commonly used therapies.
- The main findings suggest that the incremental costs associated with the specific treatment-related adverse events (with the exception of skin and subcutaneous tissue events) were substantially higher, with the 2 most expensive categories being metabolic and nutritional disorders and hematologic and lymphatic disorders and effects.
- Data from this pharmacoeconomic analysis suggest that prevention of these adverse events may be an important factor in decreasing the financial burden of existing and new therapies for metastatic melanoma.

Economic Burden Associated with Adverse Events in Patients with Metastatic Melanoma

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levels, vomiting, and stomatitis, among others. As new therapies continue to be studied and become available for the treatment of MM, it is important to fully understand the economic burden associated with AEs of existing and new therapies. A more complete understanding of these AEs will better inform economic models to more accurately characterize the overall budgetary impact of new therapies on patients and payers.

Thus, the objective of this study was to estimate the incremental health care costs of specific AEs among patients with MM treated with paclitaxel, vemurafenib, ipilimumab, dacarbazine, temozolomide, high dose IL-2, or interferon α and those known to be associated with dabrafenib and trametinib.

Methods

Study Design and Data Source

This retrospective cohort study used health care administrative claims from the MarketScan Commercial Claims and Encounters (Commercial) Database, MarketScan Medicare Supplemental and Coordination of Benefits (COB; Medicare) Database, and MarketScan Early View Database for July 1, 2004, to April 30, 2012. The Commercial Database reflects the health care experiences of the covered populations (individuals aged ≤ 64 years) of more than 100 employer and health plan clients throughout the United States. The Medicare Database contains the health care experiences of approximately 4 million retirees annually with Medicare supplemental insurance and includes the COB and the employer-paid portion of health care costs. Patients who changed from commercial to Medicare primary insurance during the study period (e.g., by turning age 65) were tracked through both databases and classified according to the first database (Commercial).

All database records were de-identified and fully compliant with U.S. patient confidentiality requirements (Health Insurance Portability and Accountability Act); therefore, the study was exempt from institutional review board approval.

Study Population

The study population was composed of patients with MM treated with 1 of 7 drug therapies (paclitaxel, vemurafenib, ipilimumab, dacarbazine, temozolomide, high dose IL-2, or interferon α monotherapy) between January 1, 2005, and April 30, 2012. The newer drug therapies, dabrafenib and trametinib, known to be associated with dabrafenib and trametinib, were not included in this analysis because their recent approval (May 2013) precluded their availability in the databases under study; however, AEs potentially associated with dabrafenib and trametinib were included in this study, specifically fever and hypertension, respectively. Patients were assigned to 1 of 7 mutually exclusive treatment cohorts based on their study drugs. Each patient entered the study once. For inclusion in the final study population, the following criteria were required:

2. A diagnosis of metastasis within 30 days before or 60 days after any MM diagnosis on nondiagnostic health care claims during the same period.
3. One or more prescription claims or outpatient service claims with a drug code (National Drug Code [NDC] number, Healthcare Common Procedure Coding System [HCPCS], or ICD-9-CM procedure code) for paclitaxel, vemurafenib, ipilimumab, dacarbazine, temozolomide, or interferon α, or 1 inpatient service claim for high dose IL-2 (ICD-9-CM procedure 00.15) on or within 365 days after the first diagnosis of MM between January 1, 2005, and April 30, 2012.

Additional inclusion criteria were (a) aged ≥ 18 years on the index date and (b) continuous enrollment with medical and pharmacy benefits during the 6 months prior to the index date.

Patients were excluded from the final study sample if (a) they had a diagnosis of nonmelanoma primary malignancy in the 6 months preceding the index date; (b) they were pregnant at any time during the entire study period; and (c) they initiated treatment on any combination regimen that included ≥ 1 of the study drugs, with the exception of combinations involving interferon α. Combinations of study drugs and other chemotherapies (e.g., paclitaxel and cisplatin) were allowed.

To maximize the sample size of the newest drugs, patients were assigned to mutually exclusive treatment groups based on the first observed claim of a study drug using the following hierarchical order: vemurafenib, ipilimumab, dacarbazine, temozolomide, high dose IL-2, paclitaxel, and interferon α (monotherapy).

Study Period

The study period comprised a pre-index period, index date, and follow-up period (Figure 1A). The date of the patient’s first prescription/infusion of the cohort’s drug after the MM diagnosis date from January 1, 2005, to April 30, 2012, was set as the index date. The 6-month period prior to the index date was designated as the baseline (pre-index) period, during which demographic and clinical characteristics were assessed. The variable length follow-up period began on the index date and continued to the end of the index treatment. Measures of health care costs and treatment characteristics were evaluated during the follow-up period.

For the AE cost analyses, the 30 days following the AE served as the time period over which health care costs were evaluated (Figure 1A). The date of the first specific AE claim served as the beginning of the 30-day period. For patients without the specific AEs, a shadow AE date was assigned by randomly sampling from the distribution of number of days from index to event for patients with the AE and then adding that number of days to the control’s index date. This ensured that controls were on the study drug of interest for a comparable amount of time as patients who developed an AE. For example, if a patient developed an AE of interest 16 days after initiating Study Drug A and was followed for an additional 30 days to ascertain costs, then the control patient was also followed for 46 days after initiating Study Drug A with cost analysis beginning after day 16.
Economic Burden Associated with Adverse Events in Patients with Metastatic Melanoma

The follow-up period (covering the study treatment episode) began on the index date for the therapy of interest and ended with the earlier of (a) a gap in therapy of ≥ 45 days, (b) switch to a new therapy, (c) inpatient mortality, (d) end of patient’s insurance eligibility, or (e) end of study period (April 30, 2012).

Outcome Variables

Adverse Events. Treatment-related AEs included those that have been associated with the 7 study drugs, as well as dabrafenib and trametinib. The selected AEs were identified from a review of each therapy’s package insert and in consultation with one of the co-authors, who is a clinical expert. The criteria for selection of specific AEs were those occurring in
TABLE 1  Categories of Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Secondary hypertension, hypertension complications, hypotension, tachycardia (including supraventricular)</td>
</tr>
<tr>
<td>CNS and psychiatric</td>
<td>Anxiety/depression, confusion, convulsions, hemiparesis, somnolence</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain, colitis, constipation, diarrhea, mucositis/stomatitis, nausea/vomiting</td>
</tr>
<tr>
<td>Hematologic and lymphatic</td>
<td>Anemia, leukopenia, neutropenia, pulmonary embolism, thrombocytopenia</td>
</tr>
<tr>
<td>Metabolic and nutritional</td>
<td>Acute renal failure; abnormal renal or liver function test; bilirubinemia; elevation of transaminase, lactate dehydrogenase, phosphatase, amylase, or lipase, hyponatremia, peripheral edema</td>
</tr>
<tr>
<td>Pain</td>
<td>Headache, myalgia/arthralgia/musculoskeletal/back/other pain, peripheral neuropathy</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Alopecia, diaphoresis (sweating), hyperkeratosis, benign neoplasms of the skin (including papilloma), photosensitivity reaction, pruritus (itching), rash, other malignant neoplasms of the skin (squamous-cell carcinoma identified separately after October 1, 2011)</td>
</tr>
<tr>
<td>Other</td>
<td>Anaphylaxis, anuria/oliguria, asthenia/fatigue, fever and/or chills, decreased appetite/anorexia, infections (including folliculitis); some AEs were combined after further review of the ICD-9-CM codes that map to each AE</td>
</tr>
</tbody>
</table>

CNS = central nervous system; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

≥ 20% of patients for any grade event or occurring in ≥ 5% of patients for grades 3 and 4. Incident AEs were identified by following patients after their index dates on 1 of the 7 study drugs. Conditions were identified by a primary or secondary diagnosis on any nondiagnostic inpatient or outpatient claim. AEs were grouped into 1 of 8 categories: (1) cardiovascular, (2) central nervous system (CNS) and psychiatric, (3) gastrointestinal, (4) hematologic and lymphatic, (5) metabolic and nutritional, (6) pain, (7) skin and subcutaneous tissue, and (8) others. A detailed description of AE categories is provided in Table 1. Because the study objective was to ascertain mean 30-day event-level AE costs, it was not necessary to require that individuals be AE-naïve prior to inclusion into the study. Patients, regardless of AE history prior to drug therapy, were included, and AEs that occurred subsequent to the index date were included in the costing analysis.

Incremental AE Costs. Incremental AE costs were defined as the difference in 30-day costs (excluding costs for study drugs and other cancer therapies) for patients with the specific AE (“cases”) and patients without the AE (“controls”). For the evaluation of each AE, all patients in the same drug cohort who did not have the event were selected as controls. The costs of each AE were evaluated across all drug cohorts.

Health care costs were the total adjudicated amount paid to all providers for inpatient and outpatient services and drugs, with the exception of study drugs and other cancer therapies. Expenditures included those made by the insurer, patient (deductible, copayment, coinsurance), and any coordination of benefits as indicated on the claim. All costs were standardized to January 2012 dollars using the medical component of the Consumer Price Index.

Baseline Characteristics. Demographic, insurance, and physician characteristics were assessed using the index drug claims. Baseline comorbidities and other clinical characteristics were assessed during the 6-month pre-index period and included the Charlson Comorbidity Index (CCI), National Cancer Comorbidity Index (NCCI), and indicator variables for baseline cancer therapies and other comorbidities of interest.

Statistical Analysis

Descriptive and multivariate analyses were conducted for this study. Unadjusted incremental AE health care costs across all patients are reported as the mean and 95% confidence interval (CI). The adjusted incremental costs of each AE were computed by estimating a multivariate regression on costs during the 30 days following the AE. Generalized linear models with a gamma-distributed error and log-link were used. Age, sex, primary payer (Medicare or commercial), insurance plan type, insurance capitation status, and NCCI were used as independent variables in the multivariate regression models. The incremental cost was estimated by the method of recycled predictions.9-11 In this method, the regression model was used to calculate a predicted 30-day cost for every patient based on the covariate values assuming the patient experienced an AE (case) and again assuming the patient did not (control); then taking the difference at the patient level, which was the estimated incremental cost; and finally averaging the incremental cost across patients.

Results

Study Sample

A total of 2,621 patients with MM who met the study selection criteria. Of the 2,621 patients, the mean age (± standard deviation [SD]) was 56.0 years (± 13.0), and 64% were male. The majority of study patients in all treatment groups lived in the North Central (28.7%) or South (36.9%) U.S. Census regions at the time of the study and carried a point-of-service insurance plan type. Nearly 90% of patients had noncapitated health plans, and approximately one-quarter of study patients were covered by Medicare. Patients in cohorts for the newer drugs vemurafenib and ipilimumab had index dates in 2011 and 2012. The remaining 5 treatment cohorts had similar index year distributions concentrated in 2005-2010, with large declines in 2011 and 2012 partly due to the selection strategy, which gave

...
priority to the newer drugs. The mean (± SD) NCCI and CCI scores during the pre-index period were 0.32 (± 0.65) and 7.89 (± 1.85), respectively (Table 3). Of the 2,621 total patients, 24% had brain cancer in the pre-index period; 34% had claims for excision surgery in the pre-index period; and approximately 43% and 34% had pre-index period hospitalization and emergency room visits, respectively. In the pre-index period, diabetes (11.7%), cardiovascular disease (9.3%), and cerebrovascular disease (8.8%) were the most common comorbid conditions.

**Cost of Adverse Events**

In descending order, the adjusted incremental AE costs were significantly greater for metabolic and nutritional disorders, hematologic and lymphatic disorders, cardiovascular, gastrointestinal, CNS, and psychiatric disorders, and pain compared with individuals without the AE (Table 4). Incremental costs associated with skin and subcutaneous tissue AEs were not significantly different between individuals with and without AEs. Detailed descriptions of costs of AEs are presented in Table 4.

### Discussion

Current treatment options for MM may be associated with considerable toxicity, which can lead to higher health care resource and associated expenditures. This retrospective cohort study is the first to estimate the health care costs of specific treatment-related AEs among patients who received commonly used therapies for MM. It is important to fully understand the economic burden of treatment-related AEs to better manage health care expenditures for existing therapies, as well as therapies in development.

The main findings from this study suggested that the incremental costs associated with the specific treatment-related AEs (with the exception of skin and subcutaneous tissue AEs) were substantially high. The 2 most expensive AE categories were (1) metabolic and nutritional disorders, and (2) hematologic and lymphatic disorders and effects. In addition, the adjusted mean costs for the AE categories analyzed, except for skin and subcutaneous tissue, among patients with AEs were at least 1.6 times higher compared with patients without AEs.

To our knowledge, no other studies have evaluated the incremental cost of specific treatment-related AEs in
between those with and without AEs. Causality of AEs to specific drug therapies in this study cannot be attributed because AEs could have been manifestations of chronic conditions or treatments not included in this study. Because the study drew upon a sample of AEs to determine their costs rather than incidence, patients with evidence of these events prior to drug therapy were included.

Moreover, the diagnosis code for MM (ICD-9-CM 172.xx) does not specify whether metastases are present. ICD-9-CM diagnosis codes are available for use for metastases, but they are not always coded on health care claims. A sensitivity analysis tested the effect on the sample size of requiring metastases diagnosis codes as an element of sample selection. When metastases codes were added as a criterion to patient selection, the size of the overall sample decreased by approximately 700 (19%). Ultimately, the requirement of a metastatic diagnosis code within 30 days prior to or 60 days after any MM diagnosis was included as part of patient selection.

In claims data, ICD-9-CM codes were used to identify AEs. These codes were not the same as those used in clinical trials; thus, the specific events that were evaluated may not directly correspond to those in trials. Furthermore, due to the specificity of ICD-9-CM codes, AEs may have been undercoded or incorrectly coded in administrative claims. In addition, AEs of mild severity may not have been reported by a provider on a medical claim. Therefore, the study may underestimate the complete cost of AEs. Findings in this study may not be representative of the whole U.S. MM population because uninsured patients and those covered by Medicaid or military-based insurance were not included in this study.

Due to the limitation of small sample sizes at the treatment group level, it was not possible to estimate specific AE costs by type of treatment. The results reported in this analysis rely on the assumption that the mean cost of specific grade 3/4 AEs are comparable regardless of the treatment that precipitated them. This remains an assumption and warrants further evaluation.

Lastly, rather than including only treatment-naïve patients (e.g., first-line patients only), the study assigned patients to treatment groups of interest by utilizing a hierarchical ordering approach in order to ensure adequate representation of the newer agents (e.g., vemurafenib and ipilimumab). As a result, approximately 15% of the patients’ index events represented second or later lines of therapy. If the risk for AE development and/or severity were to increase with later lines of therapy, there is a possibility that the mean cost of AEs could be overestimated. Given that the majority of included patients were on a first-line therapy of interest, this risk is likely minimized. Additionally, it is not certain that switching from one treatment to another increases risk of AE occurrence or severity. Given that different therapies often have different toxicity profiles, it is equally as likely for a patient to experience new and different AEs.

### Conclusions
These analyses showed that the incremental costs associated with specific AEs of the most commonly used therapies to treat
patients with MM can be substantial. Skin and subcutaneous AEs, however, were not a major driver of AE costs. Prevention of these AEs may be important for decreasing the financial burden of existing therapies and new approaches for the treatment of patients with MM.

**TABLE 4**

<table>
<thead>
<tr>
<th>Adverse Event Category</th>
<th>With AE</th>
<th>Without AE</th>
<th>Adjusted Mean</th>
<th>Incremental Costs</th>
<th>95% CI for Adjusted Incremental Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ($)</td>
<td>n</td>
<td>Mean ($)</td>
<td>With AE</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>516</td>
<td>14,693</td>
<td>1,404</td>
<td>8,077</td>
<td>14,614</td>
</tr>
<tr>
<td>CNS and psychiatric disorders</td>
<td>315</td>
<td>14,110</td>
<td>1,571</td>
<td>8,215</td>
<td>14,207</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>603</td>
<td>15,249</td>
<td>1,461</td>
<td>8,890</td>
<td>15,312</td>
</tr>
<tr>
<td>Hematologic and lymphatic disorders and effects</td>
<td>488</td>
<td>16,309</td>
<td>1,410</td>
<td>7,602</td>
<td>16,165</td>
</tr>
<tr>
<td>Metabolic and nutritional disorders</td>
<td>238</td>
<td>16,864</td>
<td>1,567</td>
<td>7,712</td>
<td>16,936</td>
</tr>
<tr>
<td>Pain</td>
<td>418</td>
<td>13,312</td>
<td>1,358</td>
<td>7,961</td>
<td>13,230</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>513</td>
<td>8,255</td>
<td>1,268</td>
<td>8,878</td>
<td>8,180</td>
</tr>
</tbody>
</table>

*Models adjusted for age, sex, primary payer (Medicare or commercial), insurance plan type, insurance capitation status, and NCCI.

Incremental costs are the difference in health care expenditures (excluding cancer drugs) between patients with the specific AEs (cases) and patients without AEs (controls).

AE = adverse event; CI = confidence interval; CNS = central nervous system; NCCI = National Cancer Comorbidity Index.

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**REFERENCES**


**DISCLOSURES**

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Arondekar, Curkendall, Monberg, Mirakhur, Lenhart, and Meyer contributed the study concept and design. Monberg and Meyer acquired the data, and Arondekar, Curkendall, Oglesby, and Lenhart performed the statistical analysis. Arondekar, Monberg, and Oglesby drafted the manuscript, and Arondekar, Curkendall, Mirakhur, and Oglesby critically revised the manuscript for important intellectual content. Arondekar, Monberg, and Mirakhur obtained funding, and Arondekar and Monberg provided administrative support. Analysis and interpretation of data and final approval of the submitted manuscript were contributed by all authors.