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Healthcare Resource Utilization and Associated Costs in Patients with Advanced Melanoma Receiving First-Line Ipilimumab

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Abstract

Background: To describe healthcare costs, excluding ipilimumab drug costs, in patients with advanced melanoma receiving ipilimumab in the US community practice setting. Methods: This was a retrospective chart review of unresectable stage III/IV melanoma patients who received first-line ipilimumab monotherapy between 04/2011 and 09/2012. Healthcare resource utilization included inpatient, emergency, specialist and hospice visits, laboratory tests, radiation, surgeries, and nursing home stays. Publicly available US unit costs were applied to each resource type to estimate costs, which were analyzed by time periods: during ipilimumab treatment, post-ipilimumab treatment (post-regimen), and within 90 days prior to death (pre-death). Generalized linear mixed models were used to explore cost predictors during the treatment period, on a per-dose-interval basis, defined as the time between ipilimumab doses. Results: Data were abstracted from 273 patient charts at 34 sites. Excluding ipilimumab drug costs, total monthly costs during the treatment regimen, post-regimen, and pre-death periods were $690, $2151, and $5123, respectively. Total healthcare costs were 27 times higher during dose intervals with a grade 3/4 adverse event compared with intervals without a grade 3/4 adverse event. Eastern Cooperative Oncology Group performance status ≥ 2 (vs 0) was also associated with significantly higher cost per dose interval. Conclusions: In this population, monthly costs exclusive of drug were significantly lower during the treatment period than in subsequent periods. Unfavorable ECOG PS was associated with significant increases in cost per dose interval. Grade 3/4 adverse events were associated with a marked increase in healthcare costs, but occurred in a small proportion of dose intervals.

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Keywords

Healthcare Resource Utilization, Ipilimumab, Melanoma

1. Introduction

The incidence of melanoma has increased dramatically in recent years, from 18.2 cases per 100,000 in 1992 to 26.3 per 100,000 in 2004 [1]. An estimated 73,870 new cases of melanoma will be diagnosed in the United States in 2015 [2]. Five-year post-surgical survival rates are approximately 80%, 70%, and 50%, respectively, for stages IIA, IIB, and IIC, and 78%, 59%, and 40% for patients with stages IIIA, IIIB, and IIIC disease [3]. Historically, the treatment of patients with advanced melanoma has been a challenge due to a lack of treatments shown to improve overall survival (OS) [4]. Prognosis has been poor for patients with metastatic disease [5], with a 1-year survival of only about 25% until recently [6].

The development of targeted pathway inhibitors and immune checkpoint modulators has provided effective new options, including the cytotoxic T-lymphocyte-associated antigen 4 inhibitor ipilimumab. A historical median survival of about 6 months [7] has recently improved significantly to rates that approaching and exceeding one year with new immune checkpoint inhibitors and molecularly targeted agents [8] [9]. Ipilimumab received US approval in March 2011 for the treatment of unresectable or metastatic melanoma, and was the first treatment to demonstrate prolonged survival in a phase III study in these patients, with a median OS of 10.1 months compared with 6.4 months for patients receiving a glycoprotein 100 peptide vaccine [8]. Moreover, a large pooled analysis has shown that ipilimumab confers long-term survival benefit in patients with advanced melanoma, with 22% of patients surviving at least 3 years and a median OS of 11.4 months [10]. These results were validated in a retrospective study conducted in a real-world setting that found a median OS of 14.5 months among patients receiving ipilimumab as first-line therapy for advanced melanoma [11].

The increasing incidence of melanoma and the development of new treatments for advanced melanoma have important and yet-unknown implications for the overall economic burden of disease. Estimates of the annual cost of treating melanoma in the United States range from $44.9 million among prevalent cases in a Medicare population to $932.5 million for newly diagnosed patients [12]-[14] However, no study has evaluated healthcare resource utilization (HCRU) and associated costs since the introduction of ipilimumab. Thus, the present analysis aimed to characterize HCRU and associated costs over the continuum of care in patients receiving first-line ipilimumab for advanced melanoma treatment, and to explore healthcare cost drivers during ipilimumab treatment.

2. Methods and Materials

2.1. Study Design

This was an analysis of HCRU and associated costs data collected from a multisite, observational chart review study of advanced melanoma patients in the United States receiving first-line treatment with ipilimumab in a real-world setting. Details of the study design and main results (effectiveness and safety data) have been published previously [11]. Ethics approval was granted by either the individual institutional review board (IRB), or by a central IRB (New England IRB, Newton, Massachusetts).

Thirty-four US sites headed by medical oncologist physician investigators participated in the study and collected data from patient medical charts at a minimum of 12 months after initiation of ipilimumab.

2.2. Patients

The study included patients diagnosed with advanced (American Joint Committee on Cancer-defined unresectable stage III or metastatic stage IV) melanoma of all primary types (cutaneous, ocular, mucosal, other, or unknown) who were ≥18 years old at diagnosis and initiated first-line treatment with ipilimumab 3 mg/kg monotherapy between April 2011 and September 2012. Patients were excluded if they had received prior systemic treatment for advanced melanoma, were currently participating or expected to participate in a trial or expanded access program, or received ipilimumab to treat a cancer other than melanoma. Patients could have received ad-

ditional therapies, including surgery, radiotherapy, or non-ipilimumab systemic therapy after the start of ipilimumab treatment, but could not initiate other therapies concomitantly with ipilimumab.

2.3. Data Collection

Detailed diagnostic, treatment, adverse event (AE), and HCRU data were collected from patient charts. Information collected at the time of diagnosis included age, disease stage, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and metastatic sites. For each dose of ipilimumab administered, serum lactate dehydrogenase, liver and thyroid function tests, blood counts, and serum creatinine were recorded, as well as ECOG PS prior to administration. Subsequent systemic regimens were also collected, including the drug, dose, route of administration, frequency, and start and end dates. AEs were coded using the Medical Dictionary for Regulatory Activities version 16.1 and graded according to the Common Terminology Criteria for Adverse Events, version 3.0 [15].

In addition to the laboratory tests and treatments described above, HCRU included referrals to specialty practitioners, hospitalizations, emergency room (ER) visits, surgeries, nursing home stays, and hospice visits.

2.4. Outcomes

The primary outcomes of the parent study included demographic and clinical characteristics, AEs, and OS in patients receiving first-line ipilimumab monotherapy. Outcomes of interest to this analysis included healthcare costs (total and by type of resource used) and predictors of healthcare costs.

Key HCRU components contributing to healthcare costs included laboratory tests during ipilimumab induction, referrals to specialty practitioners, melanoma-related hospitalizations and ER visits, subsequent post-ipilimumab systemic regimens, radiation, surgeries, nursing home stays, and hospice visits.

2.5. Data Analysis

Demographic and disease characteristics at baseline and ipilimumab dosing information were summarized for all patients. Categorical data were described using counts with percentages and continuous data by medians with ranges.

Unit costs for each type of resource in US dollars were collected from published sources. Laboratory tests, specialist visits, radiation, and ER visits were matched to Current Procedural Technology codes, and corresponding Medicare average charges were obtained [16]. Hospitalization costs were obtained from the Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality using International Classification of Diseases, 9th Revision code 172.9 (Malig Melanoma Skin Nos) [17]. The cost per hospital day was calculated by dividing total mean hospital cost by mean length of stay per HCUP, and cost per day was multiplied by the actual number of hospital days during the study to calculate total hospitalization cost. Nursing home and hospice costs were estimated using the methods of Davis *et al*. [18]. Cost of non-ipilimumab regimens were calculated using Medicare Average Sales Price for injectable medications and Wholesale Acquisition Cost for oral medications [19] [20]. Costs of investigational medications were excluded, as were the costs of supportive therapy, such as anti-emetics, analgesics, and corticosteroids, due to insufficient data to perform cost calculations. All costs were adjusted to 2014 values using the medical care component of the Consumer Price Index [21].

For each study patient, the total number of encounters of each type was divided by the total duration of follow-up to calculate the rate of resource utilization per month. Unit costs were then applied to these rates to calculate costs per type of resource per month. Monthly healthcare costs (total and by type of resource use), excluding ipilimumab drug costs, were summarized using means and standard deviations for 3 periods: treatment regimen (between first and last ipilimumab doses), post-regimen, and pre-death (within 90 days of death, among patients who died during the follow-up period). Study periods were not mutually exclusive (e.g., patients who died less than 3 months after finishing treatment had identical post-regimen and pre-death periods). Total healthcare costs between the 3 treatment periods were compared using Wilcoxon rank sum test.

Total healthcare costs for the treatment regimen were further divided into dosing intervals, defined as the period between consecutive ipilimumab doses. For this analysis, the dosing interval for the final ipilimumab dose received was defined as 21 days after the administration of that dose.

A generalized linear mixed model with random intercepts was used to explore potential predictors of costs per dose interval during ipilimumab induction. Fixed effects included occurrence of a grade 3/4 AE during the dose interval, ECOG PS prior to administration of the dose, site of melanoma, presence of brain metastases, and stage at advanced melanoma diagnosis. ECOG PS and presence of grade 3/4 AEs were determined for each dosing interval; baseline values were used for all other covariates. A gamma distribution with log link was used to account for the skewedness of cost data. A miniscule number (10^{-5}) was added to zero-cost dose intervals to avoid being excluded from regression. All statistical analyses were conducted using SAS™ v9.4 (Cary, NC, USA) with significance assessed at a two-sided level of $p < 0.05$.

3. Results

Data were abstracted from 273 patient charts at 34 sites in the South (35%), Midwest (26%), Northeast (21%), and Western (18%) regions of the United States (**Table 1**). Patients received a mean of 3.6 doses of ipilimumab (range 1 - 5 doses), with 78% of patients receiving all 4 recommended doses. At the cut-off date for data analysis (December 20, 2013), the median study follow-up was 12.2 months (interquartile range 6.6 - 15.9 months), and median OS from the start of ipilimumab therapy was 14.5 months (95% confidence interval [CI] 12.9 - 18.7 months).

All 273 patients received at least 1 dose of ipilimumab and thus contributed data to the treatment period (total 531 months of data). Of these, 142 died during follow-up and thus contributed data to the pre-death period (total 381 months of data). The post-treatment period consisted of 2250 months of data contributed by a total of 223 patients. Mean total costs, excluding ipilimumab drug costs, were $690 per month during the treatment period, with approximately equal amounts attributable to hospitalizations, surgeries, and laboratory tests (**Table 2**). During the post-regimen period, total costs were $2151 per month, half of which was comprised of subsequent systemic therapy. Costs were highest during the pre-death 90-day period at $5123 per month, with hospitalizations and hospice care comprising nearly two-thirds of the total ($p < 0.0001$).

A total of 988 dosing intervals were included in the evaluation of predictors of healthcare costs during ipilimumab induction. At least one grade 3/4 AE occurred during 77 dosing intervals (7.8%). During these 77 dosing intervals, a total of 103 grade 3/4 AEs occurred. The most common grade 3/4 AEs were enterocolitis/colitis (6.6%), fatigue (3.3%), and diarrhea (1.8%).

The generalized linear mixed model showed that total healthcare costs, excluding ipilimumab drug costs, were 27 times higher during dose intervals with a grade 3/4 AE ($p < 0.0001$) than in dosing intervals without a grade 3/4 AE (**Table 3**). ECOG PS ≥ 2 was associated with a 4.5-fold increase in costs compared with PS = 0 ($p = 0.0005$). Healthcare costs during ipilimumab induction were also higher in patients with mucosal or uveal melanoma, Stage M1 disease, and brain metastases at the initial diagnosis of advanced melanoma, but these differences were not statistically significant.

4. Discussion

This study found that monthly non-ipilimumab costs among patients with advanced melanoma were significantly lower during the treatment period than in subsequent periods. Grade 3/4 AEs were associated with a marked increase in healthcare costs during ipilimumab induction, but occurred during a small proportion of dose intervals. Worse PS was also associated with significant increases in cost per dose interval.

Estimates of monthly healthcare costs in our study are generally lower than those of real-world studies of HCRU for patients with melanoma conducted prior to the availability of ipilimumab. Reyes and colleagues conducted an analysis of healthcare costs among patients with metastatic melanoma in a large national claims database. Using data collected from 2007-2010, the study found that medical costs (excluding pharmacy costs) were $10,797 per patient per month [22]. This figure is similar to the monthly healthcare cost in our study for the pre-death period, during which healthcare costs were highest. However, the study population had a higher prevalence of brain metastases than our study (41.5% vs 12.1%), and included all-cause healthcare costs as opposed to only melanoma-related costs. An analysis of claims from 2003-2008 in a large US health insurance database found annual all-cause healthcare costs of $42,848 (or $3750 per month); however, non-drug costs were not reported separately [23]. In an analysis of the SEER-Medicare linked database, monthly all-cause healthcare costs (excluding drug costs) were $11,471 for patients with stage IV melanoma [18]. Hospitalizations and hospice care comprised a similar proportion of total costs compared with the pre-death period in our study. Hillner

Table 1. Demographic and baseline clinical characteristics.

Characteristic	Ipilimumab Patients N = 273
Male, n (%)	177 (64.8)
Race, n (%)	
White	260 (95.2)
Black	9 (3.3)
Asian	3 (1.1)
Not reported	1 (0.4)
Age at ipilimumab initiation, median years (range)	64 (26 - 91)
Primary site, n (%)	
Cutaneous	241 (88.3)
Uveal	12 (4.4)
Mucosal	5 (1.8)
Other	15 (5.5)
Stage at advanced melanoma diagnosis, n (%)	
Stage III (M0)	33 (12.1)
Stage IV (M1)	240 (87.9)
M1a	30 (11.0)
M1b	57 (20.9)
M1c	153 (56.0)
Brain metastases at advanced melanoma diagnosis, n (%)	33 (12.1)
ECOG PS at advanced melanoma diagnosis, n (%)	
0	104 (38.1)
1	116 (42.5)
≥2	19 (7.0)
Unknown	34 (12.5)

Abbreviation: ECOG, Eastern Cooperative Oncology Group; M, metastasis; PS, performance status.

Table 2. Healthcare costs during ipilimumab treatment, following treatment, and during the 3 months preceding death.

Cost Type	Period ($/month)		
	Treatment	Post-Regimen	Pre-Death
Number applicable[a]	273	223	142
Number with any healthcare cost during study period	273	137	116
Nursing home	$0 ± 0	$120 ± 1254	$878 ± 5708
Hospice	$1 ± 20	$153 ± 1116	$1369 ± 3196
Emergency room visits	$1 ± 6	$0 ± 4	$0 ± 2
Hospitalizations	$233 ± 1733	$561 ± 2212	$1784 ± 4662
Post-ipilimumab systemic therapy	Not applicable	$1080 ± 3715	$757 ± 3761
Specialist referrals	$2 ± 13	$3 ± 12	$2 ± 10
Radiotherapy	$89 ± 527	$146 ± 532	$211 ± 875
Surgeries	$190 ± 2294	$89 ± 388	$124 ± 1652
Laboratory tests during ipilimumab induction	$175 ± 343	Not applicable	Not applicable
Total mean monthly costs ($p < 0.0001$)	**$690 ± 3126**	**$2151 ± 4729**	**$5123 ± 9389**

[a]Patients who died during the treatment period contributed data only to the treatment and pre-death periods; patients who did not die contributed data to the treatment and post-treatment periods.

Table 3. Predictors of cost per dosing interval during ipilimumab induction.

Covariate	Odds Ratio (95% CI)
Grade 3/4 AE	27.9 (12.9, 60.3)
ECOG PS (reference category = 0)	
1	1.2 (0.8, 1.9)
≥2	4.5 (1.9, 10.3)
Primary site at advanced melanoma diagnosis (reference category = cutaneous)	
Uveal	1.6 (0.5, 5.4)
Mucosal	2.7 (0.5, 13.9)
Brain metastases at advanced melanoma diagnosis (reference category = no brain metastases)	1.8 (0.8, 3.9)
Stage M1 at advanced diagnosis (reference category = Stage M0)	1.5 (0.8, 2.9)

Abbreviations: AE, adverse event; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; M, metastasis; PS, performance status.

and colleagues conducted a chart review of 100 consecutive patients with metastatic melanoma treated at a single center in the United States; similar to our study, this was a medical chart review with external costs applied [24]. Non-drug costs per patient per month (converted to 2014 $) were $9127. Conversely, non-drug costs were only $25,881 from diagnosis to death or study end in a similarly designed retrospective chart review study [25], distributed over a mean follow-up period of 15 months (data on file, Bristol-Myers Squibb). While these studies suggest that healthcare costs in the pre-ipilimumab era were higher than in patients treated with ipilimumab in our study, differences in study methods and populations do not allow for a direct comparison between studies.

AEs and ECOG PS were both associated with higher healthcare costs during ipilimumab induction in this study. It is important to note that this study was unable to directly attribute costs to grade 3/4 AEs due to the lack of data on how AEs were managed or the reasons for hospitalizations and other visits. Thus, the findings illustrate healthcare costs among patients who have AEs rather than the cost attributable to the management of AEs. This distinction is important because some of the components of healthcare costs collected in this study (*i.e.*, radiotherapy) are unrelated to the treatment of AEs. Further studies are needed to evaluate the direct cost of managing AEs among patients receiving ipilimumab and other therapies.

Our study has several strengths, including the collection of real-world medical chart data and the inclusion of a clinically diverse sample of US patients with advanced melanoma receiving ipilimumab. To our knowledge, our study is the first to evaluate the temporal relationship between non-drug healthcare costs, treatment, and death in patients with advanced melanoma. The major limitation of the study is the lack of a control group, which would have allowed us to determine the degree to which the cost of ipilimumab is offset by reductions in other costs. Censoring of patients at the date of final data collection may have over-estimated healthcare costs during the post-treatment period, particularly if patients died soon after data collection. Prices of the unit costs have been estimated from published sources rather than actual transactions. Finally, it is possible that AEs were under-reported due to the retrospective study design.

It is important to place the results of this study into the rapidly-changing context of advanced melanoma treatment. After this study was conducted, the checkpoint inhibitor nivolumab was approved in the United States for use in patients with disease progression following ipilimumab and, if the patient is BRAF V600 mutation positive, a BRAF inhibitor. The approval was granted on the basis of a randomized, phase III trial in which nivolumab was associated with a 32% response rate compared with 11% among patients receiving investigator's-choice chemotherapy (ICC). Grade 3/4 AEs occurred in 9% of patients receiving nivolumab and 31% of patients receiving ICC [26]. While studies similar to ours evaluating other therapies for advanced melanoma would be needed to determine whether the impact of grade 3/4 AEs is consistent across medication regimens, our study suggests that healthcare costs could be significantly impacted by therapies associated with lower AE rates, such as nivolumab.

5. Conclusion

In conclusion, among patients with advanced melanoma treated with ipilimumab, the most significant financial burden occurs in the 90 days preceding death, which is similar to the financial burden of other malignancies [27] [28]. Grade 3/4 AEs are temporally associated with greater total healthcare costs during ipilimumab induction, and patients with worse ECOG PS incur greater healthcare expenses.

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