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Relationship between Physician-Adjudicated Adverse Events and Patient-Reported Health-Related Quality of Life in a Phase II Clinical Trial (NCT01143402) of Patients with Metastatic Uveal Melanoma*

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COMPLIANCE WITH ETHICAL STANDARDS

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Abstract

Purpose—Clinical trials commonly use physician-adjudicated adverse event (AE) assessment via the Common Terminology Criteria for Adverse Events (CTCAE) for decision-making. Patient-reported health-related quality of life (HRQoL) data is becoming more frequent in oncology; however, the relationship between physician-adjudicated AE assessment and HRQoL is understudied.

Methods—Data from a phase II trial (clinicaltrials.gov identifier: NCT01143402) where patients with metastatic uveal melanoma were randomized to receive selumetinib, an oral MEK inhibitor, or chemotherapy were analyzed. Patients reported HRQoL at baseline, after 1 month, and end of treatment (n=118), whereas physicians adjudicated AEs via CTCAE. Mean HRQoL scores were compared between patient randomization arms, as well as between those patients who did/did not receive dose modifications.

Results—Ninety-four percent had a CTCAE grade 1 for at least one treatment-associated AE, with 18% undergoing dose modification due to toxicity. Mean HRQoL scores did not significantly differ at each of the three time points. Patient and physician-adjudicated reports of nausea were significantly correlated at the start ($r=0.31$, $p<0.01$) and end of treatment ($r=0.42$, $p<0.05$). There were no significant correlations between need for dose modification and HRQoL scores.

Conclusions—Despite the high rate of physician-adjudicated AEs and need for dose modifications with selumetinib, patient-reported HRQoL was not impacted by treatment. Since HRQoL did not differ in the subgroup of patients who received dosage reductions due to AEs, patients may be willing to tolerate select AEs without dose modification (if medically appropriate). More research is needed to determine how to best integrate HRQoL data into clinical trial conduct.

Keywords

Patient-reported outcomes; Quality of life; Selumetinib; Neoplasms; Uveal Melanoma; Adverse events; Clinical trials

INTRODUCTION

As greater degrees of toxicity have been generally deemed acceptable for cancer therapies when compared with other medical indications, an essential component of clinical trials in oncology is the accurate monitoring of these AEs to help ensure patient safety and inform decision making related to treatment (Basch, 2014; Basch et al., 2015; Basch et al., 2007; Jensen & Snyder, 2016; NCI, 2001). Patients who experience clinically significant AEs, commonly defined as grade 3 or 4 toxicities as captured by the Common Terminology Criteria for Adverse Events (CTCAE (NCI, 2010)) may be required to undergo protocol mandated treatment breaks, dose modification or treatment discontinuation (Belknap,

Georgopoulos, West, Yarnold, & Kelly, 2010; Di Maio, Basch, Bryce, & Perrone, 2016). However, patients and clinicians may be willing to tolerate higher degrees of select AEs in cases where it is medically appropriate and if treatment is associated with potential meaningful improvements in clinical outcome (Trotti, Colevas, Setser, & Basch, 2007).

As part of all National Cancer Institute (NCI)-sponsored cancer clinical trials in the United States, patient AEs are adjudicated by physicians via a rating system of descriptive terms known as the CTCAE (NCI, 2010). The CTCAE consists of a descriptive library individual items that represent discrete AEs (e.g., retinal tear, neutropenia, nausea) that are adjudicated by physicians using a 5-point ordinal scale, with each of the 5-point grading levels anchored to verbiage that describes a clinical scenario that represents that given level of severity (NCI, 2010). While the CTCAE was developed and updated based on a consensus-based process that did not include a formal validation of the individual items (Trotti et al., 2003), the widespread adoption of this measure strengthens its value as a clinical assessment tool (Bruner et al., 2007).

Driven by the recent push to capture and incorporate patient-reported outcomes (PRO) data into cancer clinical trials; the United States National Cancer Institute has developed a PRO version of the CTCAE to capture AEs amenable to patient reporting (PRO-CTCAE) (Basch et al., 2014; Dueck et al., 2015; Hay et al., 2014). However, based on our recent review of the literature, the association of PRO or health-related quality of life (HRQoL) data and clinician-adjudicated AEs has not been well-established (Atkinson et al., 2016).

We therefore sought to assess patient-reported HRQoL, and the degree to which it is associated with physician-adjudicated CTCAE, to establish a better understanding of how this information may inform the clinical trial decision process. To do this, we completed a secondary analysis of data from one clinical trial of patients with advanced uveal melanoma treated with either selumetinib, an investigational inhibitor of MEK1/2, or chemotherapy (Carvajal et al., 2014). As part of this clinical trial, AEs were adjudicated by clinicians via CTCAE and patients reported their HRQoL using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M (Cormier et al., 2008)), a well-validated and widely used instrument for capturing HRQoL in patients with melanoma (Cornish, Holterhues, van de Poll-Franse, Coebergh, & Nijsten, 2009).

METHODS

Patients

The data for this analysis were obtained from a multicenter phase II trial ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01143402) identifier: NCT01143402) of patients with documented metastatic uveal melanoma who had not received prior therapy with an MEK inhibitor, temozolomide or dacarbazine who were enrolled between August 2010 and December 2013 (Carvajal et al., 2014). Eligible patients were age 18 or older; had a life expectancy > 3 months; were ambulatory (i.e., Eastern Cooperative Oncology Group performance status [ECOG PS] = 1); had measurable disease by RECIST version 1.1 (Eisenhauer et al., 2009); adequate organ function; and either untreated metastatic uveal melanoma or disease that progressed while receiving prior anticancer therapy based on physician opinion. The study protocol was approved by the

Institutional Review Boards of each participating institution. All participants provided written informed consent at time of study enrollment.

Measures

Functional Assessment of Cancer Therapy – Melanoma (FACT-M (Cormier et al., 2008))—The FACT-M is a psychometrically sound instrument that is frequently utilized to assess HRQoL in clinical trials that include patients with melanoma (Grob et al., 2015). The FACT-M consists of 43-items; 16 are specific to melanoma, with the remainder consisting of all items from the Functional Assessment of Cancer Therapy – General (FACT-G (D. F. Cella et al., 1993)). This measure yields scores for a number of subscales, including the overall FACT-General (FACT-G) total, physical (PWB), emotional (EWB), social (SWB), and functional well-being (FWB), as well as FACT-M total, a Trial Outcome Index (TOI) that is comprised of the summed PWB, FWB and FACT-M subscales, and a Melanoma Score (MS). All included patients completed this assessment independently at each specified study time point.

Common Terminology Criteria for Adverse Events version 4 (CTCAE (NCI, 2010))—The CTCAE consists of a library of 790 descriptive terms for clinician-adjudicated assessment of patient AEs related to cancer treatment. Each CTCAE term is assessed using a 5-point verbal descriptor grading scale, with each grade following a similar grading convention (i.e., 0 = not present, 1 = mild, 2 = moderate, 3 = severe and/or requiring medical intervention but not life-threatening, 4 = life-threatening consequences, and 5 = death). For the present study, diarrhea, edema, nausea, rash, and vomiting were selected as representative AEs because they are common toxicities associated with selumetinib that could conceivably make a significant impact to patient-reported HRQoL. Patient tolerance of elevated levels of these five AEs could be medically justified for continuing treatment. Nausea was the only AE assessed by both CTCAE and FACT-M.

Study Design

Enrolled patients were either randomized to receive selumetinib, an oral MEK inhibitor, at a continual dose of 75 mg twice daily or chemotherapy. Those randomized to chemotherapy could receive selumetinib at objective disease progression. AEs were formally assessed at each physician evaluation, which occurred at baseline, every 2 weeks for 4 weeks, and every four weeks thereafter. Selumetinib dosage could be reduced based on non-hematological physician-adjudicated AEs grade 3 (with the exception of alopecia) or patient platelets falling below 50,000/ μ L. Selumetinib was to be stopped for any grade 4 non-hematologic AE that a patient experienced, with the exception of alopecia, nausea or vomiting. Selumetinib administration continued if there was no evidence of disease progression and if no grade 3 or 4 non-hematologic AEs were observed. Patients reported HRQoL via the FACT-M at baseline, 1 month post-treatment, and at end of treatment.

Statistical Analysis

Independent samples *t*-tests were used to evaluate mean FACT-M scores across the baseline, 1 month post-treatment, and end of treatment time points for those patients who had a physician-adjudicated at least one AE graded 1 or higher. Comparisons were made between

patients who received selumetinib or chemotherapy, as well as those initially randomized to the chemotherapy arm who received selumetinib at disease progression, or required dose modifications due to toxicity. Multivariate analysis of variance (MANOVA) was used to compare mean FACT-M total, FACT-G total, PWB, EWB, SWB, FWB, TOI and MS scores between treatment arms, as well as between those who did or did not receive a dosage modification. Additionally, Pearson correlations were calculated to between patient-reported nausea (via FACT-M) and physician-adjudicated nausea (via CTCAE), as well as between mean FACT-M scores and whether a patient had their dose reduced due to AEs.

RESULTS

Patient Characteristics

A total of 120 patients were included in the original study sample (median age = 62; 44% female); 101 patients were randomized to receive selumetinib ($n = 50$), or chemotherapy ($n = 51$), with 19 patients receiving selumetinib without randomization. Patient characteristics are displayed in Table 1. All patients were ECOG PS 0 or 1. Nearly all patients (96%) had stage M1c disease, per American Joint Committee on Cancer cutaneous melanoma staging criteria. More than half of the sample (58%) had an elevated lactate dehydrogenase level. Twenty-three patients had previously undergone systematic therapy with ipilimumab (19%). Two patients did not complete the FACT-M at all assessment time points; therefore, the final analysis was based on 118 patients. Forty patients from the chemotherapy arm (80%) experienced disease progression and crossed over to the selumetinib arm.

Physician-Adjudicated Toxicities and Dose Modifications

Table 2 displays the percentage of patients who had physician-adjudicated CTCAE toxicities within the two randomization arms, as well as the selumetinib without randomization arm. From the entire patient sample, 94% had a physician-adjudicated CTCAE for at least one of the following treatment-associated AEs of interest: diarrhea, edema, nausea, rash, or vomiting. For those patients randomized to chemotherapy, 40% experienced CTCAE grade 1 or 2 nausea and 24% experienced grade 1 or 2 vomiting. In the selumetinib randomization study arm, at least 20% of patients experienced CTCAE grade 1 or 2 toxicity for rash (76%), diarrhea (41%), nausea (37%), edema (29%), and vomiting (22%). Rash was also the most common physician-adjudicated toxicity in the selumetinib without randomization arm (67%), with those patients also experiencing edema (56%), diarrhea (44%) and nausea (39%). Only 2 patients, both from the selumetinib randomization arm, experienced a CTCAE grade 3 toxicity of interest (edema and rash), with no grade 4 toxicities of interest observed for any of these AEs.

Twenty-two patients (18%) received a dosage modification based on physician-adjudicated AEs. Sixteen of these patients had their dosage reduced within one month (± 30 days) of completing a study assessment time point (median = 22 days, range = 0 – 197 days). Eleven patients had dosage reduced based on grade 1/2 rash. Grade 1/2 edema led to dosage reduction in two patients, whereas Grade 1/2 nausea and vomiting was responsible for dose modification in two patients. The remaining seven patients who underwent dose

modification were for various other Grade 1 or 2 non-hematologic AEs (e.g., ALT, cervical muscle weakness, dermatitis, fatigue, oral mucositis).

Health Related Quality of Life Measurements

Table 3 is a display of the FACT-M mean scores for the three assessment time points (i.e., baseline, 1 month post-treatment, and end of treatment) for those patients who had physician-adjudicated toxicity grade 1 ($n = 111$). Mean FACT-M scores did not significantly differ ($p > 0.05$) across selumetinib, chemotherapy and crossover groups. All mean FACT-M subscores (i.e., FACT-M total, FACT-G total, PWB, EWB, SWB, FWB, TOI and MS) did not differ between treatment arms (p range 0.11–0.56) or between those who did or did not receive dose modifications (p range 0.22–0.87).

We specifically assessed for any correlation between FACT-M scores and the need for dose modification due to toxicity, as those 22 individuals experiencing such toxicity might be expected to be impacted the greatest in terms of quality of life. No association with FACT-M score and the need for dose modification was observed in this population. There were no significant correlations between dose modification status and FACT-M scores ($r = 0.07$, -0.01 and 0.03 for baseline, 1 month and end of treatment, respectively). There were also no significant correlations between FACT-M scores and the timing of the dose modification (r range -0.37 – 0.16 , p 's > 0.05), as defined by the number of days since the last assessment time point (i.e., completion of the most recent FACT-M questionnaire). Patient-reported nausea was significantly correlated with physician-adjudicated nausea at time of cycle 1, week 1 ($r = 0.31$, $p < 0.01$) and at end of treatment ($r = 0.42$, $p < 0.05$).

DISCUSSION

Direct patient reporting of their symptomatic experience is an invaluable resource for understanding and monitoring treatment-related AEs as part of clinical trials in oncology (Basch, 2010). The US Food and Drug Administration (FDA) recognizes the importance of capturing this information as part of clinical outcome assessments in the drug development process (U.S. Department of Health and Human Services, 2014). The present study sought to assess patient-reported HRQoL between study arms as part of a randomized clinical trial and determine potential associations with clinician-adjudicated AEs. Despite the high rate of physician-adjudicated AEs (i.e., 94%) in this sample, patient-reported HRQoL was not significantly impacted by treatment. Patient and clinician-adjudicated assessments of nausea in this sample were statistically significantly associated, with a moderate relationship observed between these two independent rating sources. This finding is consistent with prior comparisons of patient and clinician-adjudicated AEs in other cancer disease types (Atkinson et al., 2016).

When examining HRQoL in the subgroup of patients who received dosage reductions due to AEs, we found no significant differences as compared to those who did not receive dosage reductions, with no significant associations between dosage reduction and timing (in days) since the last HRQoL assessment. This provides additional evidence that, should the context be medically appropriate, the patient may be willing to tolerate that level of AEs and continue the current dosage. Should this information be available to a given clinician in real

time, it would create an opportunity to discuss treatment options with the patient prior to any decisions being made regarding dosage reductions.

This study has a number of limitations. Uveal melanoma is a relatively rare disease type; thus would be important to replicate these results across multiple, more prevalent diseases. Additionally, it is acknowledged that despite being one of the most widely accepted instruments for the collection of HRQoL in patients with melanoma, the FACT-M was not comprehensive in assessing all AEs relevant to uveal melanoma. The only AE associated with selumetinib that was assessed by FACT-M and CTCAE was nausea. While this trial only captured patient-reported information at three study assessment time points (i.e., baseline, 1 month, and end of treatment), future work that seeks to include patient-reported AEs and HRQoL in the clinical trial decision-making process should make use of well-established methods of electronic PRO (ePRO) data capture to assess this information at the time of patient clinic visits (particularly when dose adjustments are made (Abernethy et al., 2010)), as well as between visits (Basch et al., 2016) to capture nuanced information about the patient day-to-day experience. Finally, it is acknowledged that this study may have insufficient power to detect differences in HRQoL between study arms. However, we believe that this attempt to understand how the patient-reported HRQoL may differ based on trial arm assignment, or whether dosage was modified, provides initial evidence to support the notion that this information should be considered as part of future clinical trials in oncology.

The present study illustrates the need for greater integration of patient-reporting into cancer clinical trials. Given the availability of validated patient AE reporting measures (i.e., PRO-CTCAE (Basch et al., 2014; Dueck et al., 2015; Hay et al., 2014)) and standardized item banks for reporting additional symptoms and HRQoL (e.g., Patient-Reported Outcomes Measurement Information System [PROMIS (D. Cella et al., 2010)]), clinicians now have the tools to easily and seamlessly incorporate PRO and ePRO information into their clinical trial design for comparative effectiveness research (Basch et al., 2012). Additional research is needed to determine how to best integrate patient-reported AE and HRQoL data into clinical trial conduct and ultimately use this information to inform decision-making toward improving patient care.

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Table 1

Patient Characteristics by Treatment Group

Characteristics	Randomized to Chemotherapy (n=51)	Randomized to Selumetinib (n=50)	Selumetinib without randomization (n=19)
Age - Median (range), y	62 (34–86)	62 (32–86)	63 (42–81)
Gender - Female (%)	20 (39)	34 (48)	10 (53)
ECOG Performance Status			
Median (range)	0 (0–1)	0 (0–1)	0 (0–1)
AJCC Stage, No. (%)			
M1a/b	3 (6)	2 (4)	0
M1c	48 (94)	48 (96)	17 (74)
Elevated lactate dehydrogenase level, No. (%)	30 (59)	25 (50)	14 (74)
No. of prior systemic therapies, median (range)	0 (0–2)	0 (0–3)	0 (0–2)
Ipilimumab, No. (%)	11 (22)	8 (16)	4(21)

Table 2
Physician-Adjudicated Patient (%) CTCAE Grades by Type and Treatment Group (N=120)

Adverse Events	Randomized to Chemotherapy (n=51)		Randomized to Selumetinib (n=50)		Selumetinib without randomization (n=19)	
	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Grade 1/2	Grade 3
Non-Hematologic AEs of Interest						
Diarrhea	4(8)	0	20(41)	0	8(44)	0
Edema, limbs	1(2)	0	14(29)	1(2)	10(56)	0
Nausea	20(40)	0	18(37)	0	7(39)	0
Rash	3(6)	0	37(76)	1(2)	12(67)	0
Vomiting	12(24)	0	11(22)	0	3(7)	0
Hematologic						
Anemia	8(16)	0	15(31)	0	5(28)	0
Leukopenia	9(18)	0	6(12)	0	6(33)	0
Lymphopenia	4(8)	1(2)	1(2)	3(6)	2(11)	2(11)
Neutropenia	4(8)	1(2)	3(6)	0	3(17)	0
Thrombocytopenia	8(16)	0	5(10)	0	5(28)	0
Other Non-Hematologic						
Alanine aminotransferase						
elevation	4(8)	0	17(35)	4(8)	7(39)	0
Alopecia	0	0	6(12)	0	1(6)	0
Anorexia	7(14)	0	4(8)	0	1(6)	0
Arthralgias	0	0	5(10)	0	0	0
Aspartate aminotransferase						
elevation	6(12)	0	20(41)	5(10)	7(39)	0
Blurred vision	0	0	3(6)	0	1(6)	0
Constipation	15(30)	0	3(6)	0	1(6)	0
Creatine kinase elevation	0	0	18(37)	8(16)	13(72)	1(6)
Dyspnea	0	0	7(14)	1(2)	10(56)	0
Edema, face	0	0	6(12)	0	3(17)	0
Eye disorder	0	0	4(8)	0	1(6)	0

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	Randomized to Chemotherapy (n=51)	Randomized to Selumetinib (n=50)	Selumetinib without randomization (n=19)
Fatigue	2(44)	30(61)	8(44)
Mucositis	1(2)	6(12)	0
Pruritus	0	8(16)	1(6)

Table 3

FACT-M Means (SD) for Patients with at least one CTCAE Rating ≥ 0 by Treatment Group and Assessment Time Point

	N	CTCAE ≥ 0	FACT-M			p
			Baseline	1 Month	End of Treatment	
All Patients	118	111	137.87 (21.04)	135.51 (20.68)	130.29 (25.10)	
Selumetinib	70	67	138.50 (21.22)	132.69 (21.18)	128.62 (24.05)	> 0.05
Chemotherapy	48	44	136.94 (21.00)	141.71 (18.46)	132.82 (26.89)	> 0.05
Crossover	40	38	131.96 (32.56)	134.56 (20.80)	128.04 (23.07)	> 0.05
No Dose Reduction	96	89	137.10 (21.39)	135.60 (19.53)	129.94 (25.35)	> 0.05
Dose Reduction	22	22	140.85 (19.82)	135.15 (25.51)	131.64 (24.99)	> 0.05

Note: Multivariate analysis of variance (MANOVA) was used to make within time point comparisons for selumetinib versus chemotherapy versus crossover and no dose reduction versus dose reduction. For the purposes of this study no longitudinal comparisons were made.