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Is Age $\geq$ 70 Years an Important Predictor of Adverse Events Among Patients Enrolled in Metastatic Melanoma Trials? Findings from Pooled Analyses of Therapeutic Trials

Aminah Jatoi, M.D.¹, Jacob B. Allred, M.S.², Vera J. Suman, Ph.D.², Edward T. Creagan, M.D.¹, Gary A. Croghan, Ph.D., M.D.¹, Thomas Amatruda, M.D.³, and Svetomir N. Markovic, M.D., Ph.D.¹

¹Department of Oncology, Mayo Clinic, Rochester, Minnesota

²Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

³Hubert Humphrey Cancer Center, North Memorial Hospital, Robbinsdale, Minnesota

Abstract

Background—The current study was undertaken to explore whether older age predicts adverse event rates in metastatic melanoma patients participating in cancer clinical trials.

Methods—Six phase II studies conducted at our institution for patients with metastatic disease were used in these pooled analyses: 1) ABT-510; 2) bortezomib, paclitaxel, and carboplatin; 3) everolimus; 4) bevacizumab, paclitaxel, carboplatin; 5) carboplatin and abraxane; and 6) temozolomide and everolimus. In total, 233 patients, 64 elderly (≥ 70 years) and 169 younger, were analyzed for age-based differences in grade 2 or worse adverse events and other clinical outcomes.

Results—Despite the fact that older patients had slightly worse performance scores, based on age, no differences in rates of adverse events were observed. Only worse baseline performance score predicted a higher rate of adverse events: patients with performance scores of one or worse were almost 4 times more likely to experience adverse events. Median cancer progression free survival and overall survival were comparable between older and younger patients.

Conclusion—These findings suggest that concern for adverse event rates should not preclude the enrollment of elderly melanoma patients to cancer clinical trials. Such patients should continue to be monitored carefully for tumor response and toxicity.

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Address correspondence to: Aminah Jatoi, M.D., 200 First Street SW, Rochester, Minnesota 55905, jatoi.aminah@mayo.edu.

Author Contributions

Aminah Jatoi, M.D.: conceived idea, wrote manuscript

Jacob B. Allred, M.S.: performed data analyses, edited manuscript

Vera J. Suman, Ph.D.: helped conceive idea, oversaw data analyses, edited manuscript

Edward T. Creagan, M.D.: contributed patient materials, approved manuscript

Gary A. Croghan, Ph.D., M.D.: contributed patient materials, approved manuscript

Thomas Amatruda, M.D.: contributed patient materials, approved manuscript

Svetomir N. Markovic, M.D., Ph.D.: contributed patient materials, edited and approved manuscript, provided administrative support

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Elderly patients have the highest risk for metastatic melanoma; the median age of patients who die from this malignancy is 67 years [1]. Even after adjusting for prognostic factors, elderly patients with melanoma manifest worse outcomes than their younger counterparts. In a multivariate analysis that focused on 442 consecutive patients with this malignancy, Austin and colleagues observed that only 55% of elderly patients were cancer-free at 5 years in contrast to 65% of younger patients [2]. This increased incidence of melanoma in the elderly and these worse outcomes are compounded by an increasing incidence of this malignancy [3]. In effect, healthcare providers will likely see many more elderly patients with melanoma in years to come. Taken together, these observations underscore the need to further study treatment issues directly relevant to elderly patients with this disease.

In addition to this rising incidence, previous studies suggest still more reasons to focus research on the elderly. In patients with other cancer types, elderly patients suffer higher rates of adverse events, particularly myelosuppression [4–6]. However, to our knowledge, relatively few such analyses have been conducted among elderly patients treated with newer agents, especially those that utilize targeted therapeutic approaches [4]. Because melanoma is highly immunogenic and because different classes of therapeutic agents have been tested in this disease, a focus on this malignancy allows for novel, age-based comparative assessments of adverse event profiles. The current study was therefore undertaken to explore whether adverse event profiles in melanoma patients differ based on age and whether these differences also occur among patients who have been treated with newer types of agents.

METHODS

Overview

This study was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB). It consists of analyses of six pooled, prospectively conducted clinical trials conducted at our institution in melanoma patients. These six trials had been initiated after 2003, and all received individual approval by an IRB prior to enrolling patients. If a trial had been multi-institutional in design, each participating institution had obtained IRB approval prior to the enrollment of patients.

Description of Clinical Trials

These 6 trials were selected because they all incorporated the same adverse event evaluation criteria as part of the original study protocol. Specifically, the Common Terminology Criteria, version 3 had been utilized. Patients who had central nervous system metastases were excluded because prognosis is so poor and side effects so severe in this setting; it was thought that this confounding effect might alter study conclusions.

All these trials utilized a phase II study design, tested the agents listed below, and included the following number of evaluable patients for this pooled set of analyses (Table 1): 1) ABT-510 with 21 evaluable patients (MC0375); 2) Bortezomib in combination with paclitaxel and carboplatin with 16 patients (MC047C); 3) Everolimus with 42 patients (N0377); 4) Bevacizumab in combination with paclitaxel and carboplatin with 49 patients (N047A); 5) Carboplatin and abraxane with 60 patients (N057E); and 6) Temozolomide and everolimus with 45 patients (N0675).

Details relevant to these clinical trials as well as the specific patient eligibility criteria have been reported earlier [7–10]. Briefly, in all these studies, eligible patients had to have had stage IV melanoma with measurable disease, a life expectancy viewed in months (typically greater than 3 or greater than 4 months), adequate hematology and serum chemistry laboratory results, and an Eastern Cooperative Oncology Group performance score of 2 or better.

Age Cutoff

The primary goal of the current pooled set of analyses was to compare differences in adverse events in patients who were ≥ 70 years of age versus < 70 years. This age cutoff was chosen because multiple previous studies had utilized this same threshold in defining “elderly” and also because a preliminary review of our data indicated that this threshold delineated the median age. It should be noted that many other cancer cooperative group trials had utilized the cutoff of 70 years to assess age-related differences among cancer patients [11–13].

Endpoint Definitions and Statistical Methods

The primary endpoint of the current set of analyses was to examine differences in adverse event rates based on age. A patient was considered to have had an adverse event if he/she suffered at least one of the following: 1) a grade 3+ non-hematologic adverse event; 2) a grade 4+ hematologic adverse event; 3) a grade 2+ hemorrhagic adverse event; 4) a grade 2+ neuro-motor/sensory adverse event; 5) grade 2+ hypertension; 6) grade 2+ episode of febrile neutropenia; 7) grade 2+ aspartate aminotransferase elevation; or 8) coming off-study because of any adverse event. This definition was chosen because of its clinical relevance and its clinical implications.

All adverse events were defined by the Common Terminology Criteria (CTC), version 3. Healthcare provider-reported attribution, or assessment as to whether an adverse event was related to the study drugs or not, was not taken into consideration. Using univariate logistic regression, the investigators assessed whether age (≥ 70 years of age vs. younger) predicted adverse events. The variables of sex, baseline performance score, and time-on-study (at 2 months or longer and 6 months or longer) were also tested in univariate analyses. These models were stratified based on study in order to account for inherent differences between trials.

Secondary endpoints included overall survival and cancer progression-free-survival. Time-to-event distributions were estimated with the Kaplan Meier method. Overall survival is defined as the time between patient study registration and the date of death. Cancer progression-free survival is defined as the time between patient study registration and evidence of cancer progression or death if the patient died without evidence of cancer progression.

RESULTS

Demographics

A total of 233 patients were included, and adverse event data were available for the entire cohort. The median age of the cohort as a whole was 59 years with a range of 21 to 91 years. Sixty-four percent of the cohort was comprised of men, and Eastern Cooperative Oncology Group performance scores of 0, 1, and 2 occurred in 67%, 30%, and 3%, respectively. Table 2 shows breakdowns based on age.

Cancer Treatment

Chemotherapy was utilized in 73% of patients, and a biological treatment was utilized in 74%. The median time on study was 112 days with a range of 9 to 729 days. Sixty percent of the patients were on the study for two months or longer, and 25% were on for 6 months or longer.

Adverse Events and Other Outcomes

Of the 233 patients in these 6 trials, 105 (45%) experienced at least one adverse event. Of these 105 patients, 68 (65%) had only one such event (Table 3). The number and rates of older patients with grade 3+ non-hematologic events, grade 4+ hematologic events, grade 2+ hemorrhage, grade 2+ neuromotor/sensory events, grade 2+ hypertension, grade 2+ febrile neutropenia, and grade 2+ aspartate aminotransferase were 28 (44%), 6 (9%), 1 (2%), 8 (13%), 1 (2%), 1 (2%), and 0, respectively; and, in younger patients, these respective numbers and rates were 51 (30%), 21 (12%), 5 (3%), 17 (10%), 6 (4%), 3 (2%), and 0.

There was no difference in overall adverse event rates between the 55 patients who were 70 years of age or older and the 142 younger patients. In contrast, performance score was associated with the occurrence of adverse events: those patients with performance score of one or worse were almost 4 times more likely to experience at least one of the event characteristics, as described earlier (Table 3).

Overall survival and cancer progression-free-survival were not statistically different between patients based on age, although there was perhaps a trend to suggest inferior overall survival among older patients.

DISCUSSION

This study sought differences in adverse event outcomes in older versus younger melanoma patients with metastatic disease. To our knowledge, it is the first such study to attempt to look for such age-based differences. Despite examining a total of 233 patients, who were treated with a variety of regimens, including conventional chemotherapy and biologic therapy, there were no statistically significant, age-based differences in adverse event rates. Although these pooled analyses were somewhat limited in size, we also observed no statistically significant differences in cancer-progression-free survival and overall survival.

Why are these results at odds with other studies, which have reported that older patients suffer higher rates of more severe adverse events [4–6]? Interestingly, we observed higher rates of adverse events in patients with poor performance status; we also observed a trend towards worse survival among elderly melanoma patients -- all of which are observations otherwise in keeping with what others have reported. However, it remains puzzling to us why age ≥ 70 years was not also associated with more frequent or severe adverse events. Reasons that might be invoked include the possibility that our results represent a manifestation of a philosophy that administering high-dose therapy is not a requisite for gleaning an antineoplastic effect in immunologically mediated tumors; that the mechanisms of some of the agents tested in this study, as single agents or in combination, have age-neutralizing effects; and/or that the current study was perhaps underpowered to detect a subtle increase in adverse events among elderly patients. In any case, the results reported here underscore the need for further study of adverse event profiles among the elderly, particularly among those treated with newer cancer agents.

Finally, it is important to point out that the absence of a more severe, or more frequent age-related adverse event rate does not suggest that elderly patients with melanoma do not require diligent monitoring as they receive cancer therapy. Moreover, clinical trials might potentially recruit only healthier older patients, making the conclusions drawn from this study perhaps less applicable to frail elderly patients or to a general community-based group of elderly patients with melanoma. These remarks only further underscore the need to closely monitor elderly melanoma patients who receive cancer therapy. From a clinical standpoint, our findings suggest that elderly patients should continue to be enrolled on clinical trials and monitored carefully for response and toxicity.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics. *CA Cancer J Clin.* 2008; 58:71–96. [PubMed: 18287387]
2. Austin PF, Cruse CW, Lyman G, et al. Age as a prognostic factor in the malignant melanoma population. *Ann Surg Oncol.* 1994; 6:487–94. [PubMed: 7850555]
3. Tsai S, Balch C, Lange J. Epidemiology and treatment of melanoma in elderly patients. *Nat Rev Clin Oncol.* 2010; 7:148–52. [PubMed: 20142815]
4. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non-small cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. *J Clin Oncol.* 2008; 26:60–5. [PubMed: 18165641]
5. Schild SE, Stella PJ, Geyer SM, et al. The outcome of combined-modality therapy for stage III non-small cell lung cancer in the elderly. *J Clin Oncol.* 2003; 21:3201–6. [PubMed: 12874270]
6. Argiris A, Li Y, Murphy BA, et al. Outcome of elderly patients with recurrent or metastatic head and neck cancer treated with cisplatin-based chemotherapy. *J Clin Oncol.* 2004; 22:262–8. [PubMed: 14722034]
7. Perez DG, Suman VJ, Fitch TR, et al. Phase 2 trial of carboplatin, weekly paclitaxel, and biweekly bevacizumab in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group study (N047A). *Cancer.* 2009; 115:119–27. [PubMed: 19090009]
8. Markovic SN, Suman VJ, Rao RA, et al. A phase II study of ABT-510 for the treatment of metastatic melanoma. *Am J Clin Oncol.* 2007; 30:303–9. [PubMed: 17551310]
9. Kottschade LA, Suman VJ, Amatruda T, et al. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group study N057E. *Cancer.* 2011; 117:1704–10. [PubMed: 21472717]
10. Croghan GA, Suman VJ, Maples WJ, et al. A study of paclitaxel, carboplatin, and bortezomib in the treatment of metastatic malignant melanoma: a phase 2 consortium study. *Cancer.* 2010; 116:3463–8. [PubMed: 20564112]
11. Camerini A, Valsuani C, Massoni F, et al. Phase II trial of single-agent oral vinorelbine in elderly (≥ 70 years) patients with advanced non-small cell lung cancer and poor performance status. *Ann Oncol.* 2009 Nov 13.
12. Neubauer M, Schwartz J, Caracandas J, et al. Results of a phase II study of weekly paclitaxel plus carboplatin in patients with extensive small cell lung cancer with Eastern Cooperative Oncology Group performance status of 2 or age ≥ 70 years. *J Clin Oncol.* 2004; 22:1872–7. [PubMed: 15143079]
13. Gridelli C, Perrone F, Gallo C, et al. Chemotherapy for elderly patients with advanced non-small cell lung cancer: the multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst.* 2003; 95:362–72. [PubMed: 12618501]

Figure 1.

Overall survival (OS) ($p=0.08$) and cancer progression-free survival (PFS) ($p=0.27$) were not statistically different between age-based groups.

Table 1

List of Trials

STUDY	N	REGIMEN
MC0375	21	ABT-510 100 mg subcutaneously twice a day daily (cycle length 21 days)
MC047C	16	Bortezomib 1.3 mg/m ² intravenously on days 1,4, and 8 (cycle length 21 days) Paclitaxel 175 mg/m ² intravenously on day 2 Carboplatin AUC (area under the curve) 2 on day 2 (cycle length 21 days)
N0377	42	RAD-001 10 mg orally daily (cycle length 60 days)
N047A	49	Bevacizumab 10 mg/kilogram intravenously on days 1 and 15 Paclitaxel 80 mg/m ² intravenously days 1,8, and 15 Carboplatin AUC (area under the curve) 6 on day 1 (cycle length 28 days)
N057E	60	ABI-007 100 mg/m ² intravenously days 1,8,15 Carboplatin AUC (area under the curve) 2 on days 1,8,15 (cycle length 28 days)
N0675	45	RAD-001 10 mg/day on days 1–5, 8–12, 15–19, 22–26, and 29–33 cycle 1; then 1–5, 8–12, 15–19, 22–26 after cycle 1. Temozolomide 200 mg/m ² /day orally days 8–12 cycle 1; then days 1–5 after cycle 1. (cycle length 28 days)

Table 2

Demographics Based on the 70 Years of Age Cutoff (n=233)*

	OLDER (70 years) N= 64	YOUNGER N= 169	P-value
AGE, median (range)	75 (70–91)	54 (21–69)	not reported
GENDER			
male	44 (69)	105 (62)	0.36
PERFORMANCE SCORE			
0	36 (56)	119 (70)	0.04
1 or worse	28 (44)	50 (30)	
CANCER TREATMENT**			
conventional chemotherapy	44 (69)	126 (75)	0.41
other	43 (67)	130 (77)	0.13

* Numbers in parentheses refer to percentages, unless otherwise specified.

** Percentages may not sum to 100% because patients may sometimes be included in more than one category.

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Table 3

Time-on-Study and Adverse Events for Each Clinical Trial*

	MC0375 N=21 (%)	MC047C N=16 (%)	N0377 N=42 (%)	N047A N=49 (%)	N057E N=60 (%)	N0675 N=45 (%)	Total N=233 (%)
Time on Study							
2 months	8 (38)	9 (56)	20 (48)	35 (71)	40 (67)	28 (62)	140 (60)
6 months	2 (10)	0	8 (19)	20 (41)	21 (35)	8 (18)	59 (25)
Adverse Event Characteristics							
Non-event	19 (90)	5 (31)	26 (62)	19 (39)	32 (53)	27 (60)	128 (55)
1	2 (10)	4 (25)	14 (33)	17 (35)	13 (22)	18 (40)	68 (29)
2		4 (25)	2 (5)	8 (16)	7 (12)		21 (9)
3		2 (13)		3 (6)	6 (10)		11 (5)
4		1 (6)		1 (2)	2 (3)		4 (2)
5				1 (2)			1 (<1)

* Percentages may not sum to 100% because patients may sometimes be included in more than one category.

Table 4

Associations Between Adverse Events and Candidate Clinical Variables *

Variable	Number of Patients (Adverse Events/Non Events)	Odds Ratio (95% confidence interval)	p-value
Age			
70+ years	32/32	1.58 (0.85–2.92)	0.15
<70 years	73/96		
Sex			
Female	43/41	1.45 (0.83–2.54)	0.19
Male	62/87		
Performance Score **			
0	55/100	3.75 (2.03–9.93)	<0.01
1 or worse	50/28		
Time-on-Study			
2+ months	66/74	1.01 (0.58–1.77)	0.96
<2 months	39/54		
Time-on-Study			
6+ months	29/30	0.95 (0.51–1.78)	0.87
<6 months	76/98		

* Logistic regression analyses were used and were stratified also based on clinical trial.

** Modelling utilized performance score of 1 or worse versus performance score of 0.