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Association of Gender with Efficacy of Immunotherapy in Metastatic Melanoma

Varsha Jain[1], Sriram Venigalla[1], Kevin T. Nead[1], Wei-Ting Hwang[2], John N. Lukens[1], Tara C. Mitchell[3], Jacob E. Shabason[1]*

[1]Department of Radiation Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA.
[2]Department of Biostatistics, Epidemiology and Informatics, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA.
[3]Division of Medical Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA.

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***Correspondence:**
Jacob E. Shabason, Department of Radiation Oncology, Perelman School of Medicine at the University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104, USA; Telephone No: (215) 662-6515; Fax No: (215) 349-5445; Email: jacob.shabason@uphs.upenn.edu.

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ABSTRACT

Pre-clinical data from animal models suggest that the anti-tumor efficacy of immune checkpoint blockade agents may be influenced by gender specific sex hormones. However, recent meta-analyses of clinical data aimed at addressing the impact of gender on response to these agents have demonstrated conflicting results. Given the discordant evidence, we sought to evaluate the association of gender with the receipt and efficacy of modern immunotherapies in patients with metastatic melanoma. This retrospective cohort study used the National Cancer Database to identify patients who were ≥18 years old with Stage IV melanoma from 2011 to 2015. Patterns of utilization of immunotherapy, including by gender, were assessed using multivariable logistic regression. A multivariable Cox proportional hazards model, including an interaction term between the receipt of immunotherapy and gender, was used to evaluate whether gender modified the association of receipt of immunotherapy with hazards of death. 11,944 patients met study inclusion criteria. Of these, 8,093 (68%) were males and 3,851 (32%) were females. 2,930 (25%) patients received immunotherapy while 9,014 (75%) did not. There was no statistically significant difference in the receipt of immunotherapy between males and females. On multivariable analysis, receipt of immunotherapy was associated with a survival benefit in both males and females. However, a statistically significant difference in efficacy of immunotherapy based on gender was not observed ($p_{interaction}$ =0.422). Utilizing a real world cohort of patients derived from a national cancer registry, gender was not associated with differences in immunotherapy survival outcomes in patients with metastatic melanoma.

Introduction

Modern immunotherapy agents targeting cellular immune checkpoint pathways have demonstrated promising survival outcomes in metastatic melanoma, and are now the standard of care[1,2]. While these drugs hold the promise of offering durable tumor control, only a fraction of treated patients respond. Understanding the clinical and biological factors (such as gender) that may modulate response to these agents is imperative to better select the most efficacious therapies for a particular patient as well as to inform future clinical trials.

Pre-clinical data from animal models does suggest sex hormone based modulation of immune pathways[3,4]. However, recent meta-analyses evaluating gender-associated differences in response to modern immunotherapies in advanced cancers have shown conflicting results[5-7].

Given this area of clinical controversy, we evaluated a real world cohort of patients with metastatic melanoma derived from a national cancer registry to examine the association of gender with the receipt of and survival outcomes with immunotherapy.

Methods

This study was exempt from review by our institutional review board as we used a de-identified dataset. We included patients who were ≥18 years, had Stage IV (metastatic) cutaneous melanoma, and were diagnosed from 2011- 2015. This time period was chosen given the approval of Ipilimumab, the first modern immune checkpoint inhibitor (ICI) for metastatic melanoma, in 2011. Patients were excluded if receipt of immunotherapy or the disease stage was unknown or missing (eFigure 1).

Baseline characteristics between patients who did and did not receive immunotherapy were compared using Pearson's χ^2 test. A multivariable logistic regression model was utilized to evaluate the patterns of receipt of immunotherapy.

In order to determine if the association of receipt of immunotherapy with hazards of death was modified by gender, a multivariable Cox proportional hazards model which included an interaction term between receipt of immunotherapy (yes/no) and gender (male/female) was used. The same model as above was used to derive individual hazards of death associated with receipt of immunotherapy for males and females as listed in Table 3.

All baseline covariates (Table 1) were evaluated. Covariates achieving a threshold significance of $p<0.1$ on univariate analysis were included in multivariable logistic regression and Cox proportional hazards analyses (Table 2 and eTable 1, respectively).

Propensity score (PS) adjustment with robust variance estimation was used to further adjust for potential confounding factors[8] and denoted the probability of

Table 1: Baseline patient characteristics

Receipt of Immunotherapy	No	%	Yes	%	Total	%	chi2
Total, n	9,014	(75)	2,930	(25)	11,944	(100)	
Gender							0.796
Male	6,102	(68)	1,991	(68)	8,093	(68)	
Female	2,912	(32)	939	(32)	3,851	(32)	
Age							<0.001
18-49	1,187	(13)	558	(19)	1,745	(15)	
50-69	3,921	(43)	1,473	(50)	5,394	(45)	
≥70	3,906	(43)	899	(31)	4,805	(40)	
Race							0.425
Non-Hispanic White	8,490	(94)	2,767	(94)	11,257	(94)	
Non-Hispanic Black	133	(1)	35	(1)	168	(1)	
Hispanic	238	(3)	70	(2)	308	(3)	
Other	153	(2)	58	(2)	211	(2)	
Facility Area							0.001
Metropolitan	7,181	(80)	2,427	(83)	9,608	(80)	
Urban	1,394	(15)	369	(13)	1,763	(15)	
Rural	193	(2)	50	(2)	243	(2)	
Unknown	246	(3)	84	(3)	330	(3)	
Insurance							<0.001
Commercial	2,954	(33)	1,314	(45)	4,268	(36)	
Medicare	4,535	(50)	1,208	(41)	5,743	(48)	
Medicaid	711	(8)	194	(7)	905	(8)	
Uninsured	486	(5)	105	(4)	591	(5)	
Other	328	(4)	109	(4)	437	(4)	
Zip Code Education Level							<0.001
≥21%	1,309	(15)	300	(10)	1,609	(13)	
13%-20.9%	2,250	(25)	690	(24)	2,940	(25)	

7%-12.9%	3,083	(34)	1,032	(35)	4,115	(34)	
<7%	2,345	(26)	903	(31)	3,248	(27)	
Unknown	27	(<1)	5	(<1)	32	(<1)	
Zip Code Median Income							<0.001
<38,000	1,311	(15)	337	(12)	1,648	(14)	
38,000-47,999	2,168	(24)	612	(21)	2,780	(23)	
48,000-62,999	2,512	(28)	857	(29)	3,369	(28)	
≥63,000	2,983	(33)	1,119	(38)	4,102	(34)	
Unknown	40	(<1)	5	(<1)	45	(<1)	
Facility Type							<0.001
Non-Academic	5,367	(60)	1,297	(44)	6,664	(56)	
Academic	3,215	(36)	1,404	(48)	4,619	(39)	
Unknown	432	(5)	229	(8)	661	(6)	
Facility Location							<0.001
East	1,591	(18)	622	(21)	2,213	(19)	
South	3,317	(37)	880	(30)	4,197	(35)	
Central	2,042	(23)	669	(23)	2,711	(23)	
West	1,632	(18)	530	(18)	2,162	(18)	
Unknown	432	(5)	229	(8)	661	(6)	
Charlson Deyo Score							<0.001
0	6,662	(74)	2,410	(82)	9,072	(76)	
1	1,608	(18)	398	(14)	2,006	(17)	
2	484	(5)	91	(3)	575	(5)	
3	260	(3)	31	(1)	291	(2)	
Surgery to Metastatic site							0.03
No	6,542	(73)	2,068	(71)	8,610	(72)	
Yes	2,404	(27)	829	(28)	3,233	(27)	
Unknown	68	(1)	33	(1)	101	(1)	
Brain Metastasis							<0.001
None	4,544	(50)	1,480	(51)	6,024	(50)	
Present	2,425	(27)	632	(22)	3,057	(26)	
Unknown	2,045	(23)	818	(28)	2,863	(24)	
Liver Metastasis							<0.001
None	5,441	(60)	1,605	(55)	7,046	(59)	
Present	1,474	(16)	505	(17)	1,979	(17)	
Unknown	2,099	(23)	820	(28)	2,919	(24)	
Lung Metastasis							<0.001
None	4,036	(45)	1,111	(38)	5,147	(43)	
Present	2,893	(32)	999	(34)	3,892	(33)	
Unknown	2,085	(23)	820	(28)	2,905	(24)	
Bone Metastasis							<0.001
None	5,646	(63)	1,697	(58)	7,343	(61)	
Present	1,287	(14)	416	(14)	1,703	(14)	
Unknown	2,081	(23)	817	(28)	2,898	(24)	
Receipt of Chemotherapy							<0.001
No	6,094	(68)	2,549	(87)	8,643	(72)	
Yes	2,620	(29)	336	(11)	2,956	(25)	

Unknown	300	(3)	45	(2)	345	(3)	
Receipt of Radiotherapy							<0.001
No	5,778	(64)	1,740	(59)	7,518	(63)	
Yes	3,166	(35)	1,184	(40)	4,350	(36)	
Unknown	70	(1)	6	(<1)	76	(1)	
Year of Diagnosis							<0.001
2011	1,859	(21)	341	(12)	2,200	(18)	
2012	1,811	(20)	356	(12)	2,167	(18)	
2013	1,881	(21)	559	(19)	2,440	(20)	
2014	1,801	(20)	707	(24)	2,508	(21)	
2015	1,662	(18)	967	(33)	2,629	(22)	

Table 2: Adjusted odds associated with the receipt of immunotherapy in patients with metastatic melanoma

	Adjusted Odds ratio	**95% Confidence Interval**		**p-value**
Gender				
Male	[reference]			
Female	0.92	0.83	1.01	0.077
Age	0.96	0.96	0.97	<0.001
Facility Area				
Metropolitan	[reference]			
Urban	0.74	0.64	0.87	<0.001
Rural	0.74	0.52	1.05	0.095
Unknown	0.93	0.71	1.23	0.619
Insurance				
Commercial	[reference]			
Medicare	0.97	0.85	1.11	0.672
Medicaid	0.54	0.45	0.66	<0.001
Uninsured	0.49	0.38	0.62	<0.001
Other	0.79	0.61	1.02	0.075
Zip Code Education Level				
≥21%	[reference]			
13%-20.9%	1.31	1.10	1.55	0.002
7%-12.9%	1.30	1.08	1.55	0.005
<7%	1.41	1.15	1.72	0.001
Zip Code Median Income				
<38,000	[reference]			
38,000-47,999	1.00	0.84	1.19	0.989
48,000-62,999	1.07	0.90	1.28	0.457
≥63,000	1.08	0.89	1.32	0.429
Facility Type				
Non-Academic	[reference]			

Academic	1.63	1.48	1.81	<0.001
Unknown	0.80	0.62	1.03	0.087
Facility Location				
East	[reference]			
South	0.83	0.72	0.95	0.006
Central	0.95	0.82	1.09	0.452
West	0.99	0.85	1.16	0.937
Distance from Treatment Facility				
≤40 miles	[reference]			
>40 miles	1.46	1.28	1.66	<0.001
Unknown/Missing	1.25	0.35	4.48	0.729
Charlson Deyo Score				
0	[reference]			
1	0.77	0.68	0.88	<0.001
2	0.57	0.44	0.72	<0.001
3	0.34	0.23	0.50	<0.001
Surgery to Metastatic Site				
No	[reference]			
Yes	0.95	0.85	1.05	0.332
Unknown	1.35	0.84	2.18	0.214
Brain Metastasis				
None	[reference]			
Present	0.59	0.52	0.67	<0.001
Unknown	1.28	0.80	2.06	0.307
Liver Metastasis				
None	[reference]			
Present	1.28	1.12	1.46	<0.001
Unknown	0.87	0.53	1.42	0.577
Lung Metastasis				
None	[reference]			
Present	1.58	1.42	1.77	<0.001
Unknown	1.32	0.86	2.01	0.202
Bone Metastasis				
None	[reference]			
Present	0.96	0.83	1.11	0.580
Unknown	0.99	0.59	1.65	0.961
Receipt of Chemotherapy				
No	[reference]			
Yes	0.22	0.19	0.25	<0.001
Unknown	0.35	0.25	0.49	<0.001

Receipt of Radiation				
No	[reference]			
Yes	1.56	1.40	1.74	<0.001
Unknown	0.42	0.17	1.00	0.050
Year of Diagnosis				
2011	[reference]			
2012	1.05	0.88	1.24	0.610
2013	1.62	1.39	1.90	<0.001
2014	2.22	1.91	2.59	<0.001
2015	3.32	2.85	3.85	<0.001

Table 3: Overall survival associated with immunotherapy in patients with metastatic melanoma[1]

	Multivariable			PS analysis		
Gender	**HR [95% CI]**	**p-value**	**$P_{interaction}$**	**HR[95% CI]**	**p-value**	**$P_{interaction}$**
Male	0.56 [0.52, 0.61]	<0.001		0.56 [0.51, 0.62]	<0.001	
Female	0.62 [0.55, 0.70]	<0.001		0.61 [0.53, 0.70]	<0.001	
			0.422			0.414

HR= Hazards Ratio, CI = Confidence interval, PS= Propensity Score

[1]Refer to eTable 1 for a detailed list of covariates included in the multivariable model

receiving immunotherapy(matched for all covariates listed in eTable1). A two-tailed *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata SE, version 15.0 (StataCorp, College Station, TX).

Results

A total of 11,944 patients met study inclusion criteria. Of these, 2,930 (25%) received immunotherapy while 9,014 (75%) did not. There were 8,093 (68%) males and 3,851 (32%) females. The median age of the patient cohort was 66 years (range: 55-76 years). Detailed baseline patient characteristics are listed in Table 1.

25% of the males and 24% of the females received immunotherapy. On multivariable logistic regression analysis, there was no statistically significant difference in the receipt of immunotherapy between males and females (OR: 0.92, 95% CI: 0.83-1.01, p=0.077). Factors associated with an increased likelihood of receiving immunotherapy included treatment at academic centers, presence of extra-cranial metastatic disease (liver, lung or bone), and a later year of diagnosis. Conversely, factors associated with a decreased likelihood of receiving immunotherapy included having Medicaid and being uninsured (vs. commercial insurance), having a higher Charlson Deyo comorbidity score, receiving chemotherapy, and having brain metastases (Table 2).

On multivariable survival analysis, receipt of immunotherapy was associated with a survival benefit in both males (HR: 0.56, 95% CI: 0.52-0.61, p<0.0001) and females (HR: 0.62, 95% CI: 0.55-0.70, p<0.001). However, the interaction term testing whether the hazards of death associated with the receipt of immunotherapy is modified by gender was not significant ($p_{interaction}$=0.422); highlighting that there was no statistically significant difference in efficacy of immunotherapy based on gender (eTable 1). These findings were consistent on PS matched analysis (Table 3).

Discussion

We utilized the NCDB to examine the association between gender and receipt and efficacy of modern immunotherapies in a real world cohort of patients with metastatic melanoma. Our results show that there was no difference in the likelihood of receipt of immunotherapy between males and females. Additionally, while immunotherapy was associated with a significant survival benefit in both males and females, we did not observe a statistically significant difference in efficacy based on gender.

Consistent with the trend of increased adoption of ICIs for management of metastatic melanoma, we noted an increased likelihood of receiving immunotherapy in recent years [9]. We also observed that patients with brain metastases were less likely to receive immunotherapy as this cohort had been disproportionately excluded from initial melanoma clinical trials [10]. Lastly, disparities in adoption of modern therapies between academic vs. community centers has been well documented for other treatments [11] and was also highlighted in our analyses.

Recent research to evaluate if there is a meaningful clinical difference in response to ICIs by gender has resulted in conflicting results. Specifically, Conforti et al[6] performed a meta-analysis of 20 prospective studies across numerous disease sites and found that males respond better than females when treated with both cytotoxic T lymphocyte associated protein-4 (CTLA-4) and programmed death protein-1 (PD-1) inhibitors. However, a recent meta-analysis published by Wallis et al[5] failed to find a statistically significant association of gender with the efficacy of ICIs in multiple advanced cancers. Similar to the study by Wallis et al, our findings also suggest that the efficacy of immunotherapy does not differ on the basis of gender. Given the controversy in the aforementioned published meta-analyses of prospective clinical trials, our study contributes additional information regarding the association of gender with the efficacy of immunotherapy. Furthermore, our dataset derives from a large (>10,000) heterogeneous sample of patients treated at more than 1,500 Commission on Cancer accredited facilities [12] across the United States, includes individual level patient data and simulates real life practice patterns.

Limitations

Our study has several key limitations. First, there is inherent selection bias given the retrospective nature of the analysis. To minimize this bias, we performed PS-weighted analysis to adjust for a range of measured confounders. Second, the NCDB does not specify the type of immunotherapy used and hence definitive conclusions about the agents that were administered such as therapies targeting CTLA-4 and PD-1/PD-L1, Interleukin-2, Interferon-α etc. cannot be drawn. Given the above limitation, we only included patients treated after the approval of the first ICI (ipilumumab) in 2011 for metastatic melanoma. Furthermore, the term immunotherapy as coded by the NCDB can refer to other antibody based therapies, but these are not approved for use in melanoma and therefore if present would only represent a small minority of patients. Lastly, we lacked information about dosage, treatment schedules, duration of treatment, and toxicity which may have contributed to the outcomes.

Conclusions

We demonstrate that in the era of ICIs, there does not appear to be a difference between men and women in the likelihood of receipt of immunotherapy for metastatic melanoma. Additionally, while the receipt of immunotherapy was associated with a survival benefit for both men and women, we did not observe a statistically significant difference in survival outcomes based on gender. These findings further inform the controversy regarding the efficacy of immunotherapy based on gender by contributing real world data from a national cancer registry. Future and ongoing clinical trials utilizing ICIs and other immune modulating agents should further evaluate gender specific responses.

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