© Curr Gynecol Oncol 2020, 18 (2), p. e39–e42
DOI: 10.15557/CGO.2020.0008

Received: 10.12.2020
Accepted: 21.12.2020
Published: 31.12.2020

Sheida Naderi-Azad[1], Faisal Sickander[2], Rossanna C. Pezo[3,4]

Immunotherapy toxicities in metastatic vulvar and vaginal melanomas: a retrospective cohort study

Toksyczność immunoterapii w przerzutowych czerniakach sromu i pochwy: retrospektywne badanie kohortowe

[1] Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[2] Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
[3] Division of Medical Oncology and Hematology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[4] Department of Medicine, University of Toronto, Toronto, ON, Canada
Correspondence: Rossanna Pezo MD, PhD, FRCP, Division of Medical Oncology and Hematology, Sunnybrook Odette Cancer Centre, 2075 Bayview Avenue, Toronto, ON, Canada, M4N 3N5, e-mail: rossanna.pezo@sunnybrook.ca

Abstract

This retrospective cohort study examined the factors for patients with metastatic vulvar and vaginal melanomas on immune checkpoint inhibitors. The study included all patients over the age of 18 who received either anti-cytotoxic T-lymphocyte-4 (anti-CTLA-4) therapy or anti-programmed cell death protein-1 (anti-PD-1) therapy at the Sunnybrook Hospital from June 2012 to December 2018. There were 11 patients with vulvar or vaginal melanoma on immune checkpoint inhibitor therapy. The main sites of metastasis included the lungs, lymph nodes, soft tissues, and liver. The majority of patients received prior radiation therapy (7/11) and prior surgical therapy (9/11). There were no differences in overall survival for vulvar or vaginal melanomas on anti-PD-1 vs. anti-CTLA-4 therapy ($p > 0.05$). There were no significant differences in overall survival for vulvar and vaginal vs. cutaneous melanoma ($p > 0.5$). There were no significant differences in overall survival in patients with vulvar and vaginal melanoma in the presence vs. absence of immune-related adverse events ($p > 0.05$), yet there was a significant difference in patients with cutaneous melanoma in the presence vs. absence of immune-related adverse events ($p < 0.05$). Knowledge of the presentation and outcome of vulvar and vaginal melanomas is important for clinical practice in gynecology.

Keywords: immune-related adverse events, metastatic melanoma, vulvar and vaginal melanoma, immune checkpoint inhibitors

Streszczenie

W retrospektywnym badaniu kohortowym ocenie poddano pacjentki z przerzutowym czerniakiem sromu i pochwy leczone inhibitorami immunologicznego punktu kontrolnego. Do badania kwalifikowały się pacjentki powyżej 18. roku życia, u których w Sunnybrook Hospital w okresie od czerwca 2012 do grudnia 2018 roku stosowano terapię blokującą antygen-4 cytotoksycznych limfocytów T – CTLA-4 (terapię anty-CTLA-4) lub leczenie przeciwciałami skierowanymi przeciwko receptorowi programowanej śmierci komórki 1 (terapię anty-PD-1). Do badania włączono 11 pacjentek z czerniakiem sromu lub pochwy leczonych inhibitorami immunologicznego punktu kontrolnego. Przerzuty były umiejscowione głównie w płucach, węzłach chłonnych, tkankach miękkich i wątrobie. U większości pacjentek wcześniej stosowano radioterapię (7/11) i leczenie chirurgiczne (9/11). Nie stwierdzono różnic w przeżyciu całkowitym u pacjentek z czerniakami sromu i pochwy otrzymujących terapię anty-PD-1 i terapię anty-CTLA-4 ($p > 0,05$). Nie odnotowano znamiennych różnic pod względem przeżycia całkowitego u pacjentek z czerniakiem sromu i pochwy w porównaniu z czerniakiem skóry ($p > 0,5$). Ponadto nie stwierdzono znamiennych różnic w przeżyciu całkowitym u pacjentek z czerniakiem sromu i pochwy w związku z obecnością/brakiem zdarzeń niepożądanych pochodzenia immunologicznego ($p > 0,05$), jednak znamienną różnicę w zależności od obecności/braku zdarzeń niepożądanych pochodzenia immunologicznego ($p < 0,05$) odnotowano wśród pacjentek z czerniakiem skóry. Wiedza na temat obrazu klinicznego i wyników leczenia czerniaków sromu i pochwy jest istotna dla praktyki klinicznej w obszarze ginekologii.

Słowa kluczowe: zdarzenia niepożądane pochodzenia immunologicznego, przerzutowy czerniak, czerniak sromu i pochwy, inhibitory immunologicznego punktu kontrolnego

INTRODUCTION

The use of immunotherapy for the treatment of metastatic melanoma was initially started with the approval of anti-cytotoxic T-lymphocyte-4 (anti-CTLA-4) therapy which was the first therapy to improve overall survival (OS) in patients with metastatic melanoma[1]. Furthermore, anti-programmed cell death protein-1 (anti-PD-1) therapy was approved by the Food and Drug Administration for the management of advanced melanoma upon evidence of their unprecedented response rates of 30–40% in various clinical trials[2]. Anti-CTLA-4 antibodies block the interaction between CTLA-4 (cytotoxic T-lymphocyte-associated protein-4) molecules on the surface of T cells and B7 receptors[3], while anti-PD-1 antibodies block the interaction between PD-1 receptors[4]. Vulvar and vaginal melanomas comprise a subgroup of mucosal melanoma associated with high rates of recurrence and distant metastases. They have a poor prognosis, in part due to the lack of well-established protocols for staging and treatment, as well as difficulties performing full surgical resection for advanced presentations[5]. In view of the rare incidence of these melanomas, data on clinical presentation and treatment outcome for these melanomas is largely available through case reports and small retrospective studies[6]. As there are few comprehensive studies that examine patients metastatic vulvar and vaginal melanomas on anti-PD-1 and anti-CTLA-4 therapies[6,7], we have investigated the clinical presentation, disease management, and clinical outcomes for these immunotherapeutic agents.

MATERIALS AND METHODS

The study inclusion criteria were patients with metastatic melanoma at least 18 years old that received immune checkpoint inhibitors (ICIs) (either anti-PD-1 and/or anti-CTLA-4 therapy) at the Sunnybrook Hospital from June 2012 to December 2018. There were no specific exclusion criteria. Research Ethics Approval was obtained from the Sunnybrook Health Sciences Centre. The primary outcome included the clinical presentation and management of vulvar and vaginal melanomas. The secondary outcomes included the clinical outcome in vulvar and vaginal melanomas treated with ICIs. Descriptive statistics were used to summarize data. Chi-square test was used to determine associations. Kaplan–Meier analysis and log-rank test were used for OS. p-values <0.05 were considered statistically significant.

RESULTS

From 235 patients with metastatic melanoma, 11/235 (4.7%) had vulvar and vaginal melanomas, 173/235 (73.6%) cutaneous melanoma, and the remainder other subtypes. Patients with vulvovaginal melanoma had a median age of 58.0 years (range 29.0–78.0). The clinical features and treatments for vulvar and vaginal melanomas are depicted in Tab. 1. Most patients who received radiation therapy were also treated surgically.

There were no significant associations between types of toxicities and sites of metastasis including lung metastases and pneumonitis (p = 0.2), liver metastases and gastrointestinal toxicity (p = 0.4), central nervous system metastases and nervous system toxicity (p = 0.1), musculoskeletal/connective tissue disease metastases, and soft tissue/other toxicities (p = 0.1). Furthermore, there were no differences in OS for vulvar or vaginal melanomas on anti-PD-1 (46.0 months) vs. anti-CTLA-4 therapy (45.3 months; p > 0.05). There were

Clinical features and treatment data	***n* (%)**
Melanoma	
Vaginal	7/11 (63.6%)
Vulvar	4/11 (36.4%)
Mutation status	
NRAS	1/11 (9.1%)
c-*KIT*	1/11 (9.1%)
BRAF	0/11 (0%)
Site of metastasis	
Lung	9/11 (81.8%)
Lymph node	9/11 (81.8%)
Soft tissue	7/11 (63.6%)
Liver	6/11 (54.5%)
Central nervous system	2/11 (18.2%)
Bone	2/11 (18.2%)
irAEs	
Gastrointestinal	2/11 (18.2)
Cutaneous	1/11 (9.1)
Pneumonitis	1/11 (9.1)
Hypothyroidism	1/11 (9.1)
Nervous system disorder	1/11 (9.1)
Renal and urinary disorder	1/11 (9.1)
Musculoskeletal and connective tissue disorder	1/11 (9.1)
Prior treatment	
Adjuvant systemic therapy (paclitaxel/carboplatin)	1/11 (9.1%)
Adjuvant interferon	4/11 (36.4%)
Surgery only	9/11 (81.8)
Radiation therapy only	7/11 (63.6%)
First line ICI therapy for unresectable/metastatic disease	
Anti-PD-1	5/11 (45.5%)
Anti-CTLA-4	5/11 (45.5%)
Treatment outcome	
Progressive disease	6/11 (54.5%)
Response to treatment	1/11 (9.1%)
Missing data	4/11 (36.4)

anti-CTLA-4 – anti-cytotoxic T-lymphocyte-associated protein-4; **anti-PD-1** – anti-programmed cell death protein-1; ***BRAF*** – human gene that encodes the protein B-raf; ***c-KIT*** – human gene that encodes the receptor kinase protein known as tyrosine-protein kinase KIT; **ICI** – immune checkpoint inhibitor; **irAEs** – immune-related adverse events; ***NRAS*** – human gene that encodes the protein N-Ras.

Tab. 1. Clinical features and treatments for vulvar and vaginal melanomas

DOI: 10.15557/CGO.2020.0008

no significant differences in OS for vulvar and vaginal vs. cutaneous melanoma ($p > 0.5$). Furthermore, OS was not different in patients with vulvar and vaginal melanomas with and without immune-related adverse events (irAEs) ($p > 0.05$), but was significantly different in cutaneous melanoma with and without irAEs ($p < 0.05$).

DISCUSSION

In summary, our results included 11 patients with vulvar or vaginal melanoma on ICI therapy. These patients developed irAEs and metastases that affected a wide variety of organ systems. The majority of patients received prior radiation therapy and prior surgical treatment. Furthermore, there were no significant differences in OS for vulvar and vaginal vs. cutaneous melanoma. Lastly, there were no significant differences in OS in patients with vulvar and vaginal melanoma in the presence vs. absence of irAEs ($p > 0.05$), yet a significant difference was noted in patients with cutaneous melanoma in the presence vs. absence of irAEs ($p < 0.05$).

Literature findings correlate with ICI-induced irAEs such as colitis, dermatitis and hypophysitis[6,7], alongside additional irAEs such as vulvitis[8]. The ICI therapies were generally well-tolerated, as demonstrated by the low incidence of irAEs, a result that is further supported by other previous studies[6]. Importantly, however, many irAEs can present asymptomatically or with non-specific, mild-grade symptoms, thus necessitating the importance of educating providers about the distinct toxicity profiles of irAEs in this patient population despite unassuming initial clinical presentations[9–11]. The management of ICI-induced-irAEs in patients with vulvar and vaginal melanoma has ranged from the discontinuation of ICI therapy, and the switch from combination therapy to monotherapy, to the provision of steroids[12].

Furthermore, radiation is more commonly used in disease management due to difficulties obtaining clear surgical margins. Recent studies indicate better outcomes in patients treated with surgery or combination therapy, as compared to radiation monotherapy[13], explaining the high number of patients receiving both radiation and surgical therapy prior to ICIs. Of note, complete surgical resection in unattainable in many cases of vulvar and vaginal melanoma due to the advanced disease presentation[5]. In addition, radical surgeries usually require a long recovery period in the vulvar and vaginal region, as well as the associated lymph nodes[14]. Thus, efforts towards earlier diagnosis of vulvar and vaginal melanomas may contribute to a more effective treatment of these melanomas. As clinical management in highly dependent on tumor stage[15,16], and may include other modalities such as chemotherapy and targeted therapy[17], future studies can compare the number of prior radiation vs. surgical therapies in these patients prior to ICI therapy.

While our data showed no significant difference in survival for vulvar and vaginal vs. cutaneous melanoma, other studies suggest a worse prognosis for vulvar and vaginal melanomas[18]. Furthermore, the survival of vaginal melanoma specifically is inferior to that of vulvar melanoma due to histopathological differences[19]. Therefore, the ratio of vulvar to vaginal melanomas may have affected our results.

The ICI-induced-irAEs are postulated to be caused by the systemic activation of cytotoxic lymphocytes that target healthy tissues[20]. Our results showed significant differences in OS in the presence and absence of irAEs for cutaneous melanoma but not vulvar or vaginal melanomas. The finding suggests that while irAEs were historically associated with improved survival in cutaneous melanoma, this survival benefit might not necessarily translate to rare subtypes of mucosal melanoma such as vulvar and vaginal melanomas. Increasing education about the presentation of irAEs and disease outcome could serve as a vital touchpoint for patients with vulvar and vaginal melanomas on ICI therapy. Future studies can examine whether irAE sites and severity affect disease outcome in vulvar and vaginal melanomas. With the increasing use of ICIs for vulvar and vaginal melanomas, knowledge of the presentation and outcomes is important for routine clinical practice in gynecology.

Conflict of interest

Rossanna C. Pezo reports the receipt of honoraria from Pfizer, EMD Serono and Novartis, and research funding from Merck, and serves on advisory boards for Astra Zeneca, Exact Sciences, Lilly, Myriad Genetics, Pfizer and Novartis, all outside the submitted work. The other authors report no conflicts of interest.

Funding/Support and role of the sponsor

This work was supported by a Strategic Innovation Grant from the University of Toronto, Division of Medical Oncology to Rossanna C. Pezo.

References

1. Wolchok JD, Chiarion-Sileni V, Gonzalez R et al.: Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017; 377: 1345–1356.
2. Gong J, Chehrazi-Raffle A, Reddi S et al.: Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. J Immunother Cancer 2018; 6: 8.
3. Mihajlovic M, Vlajkovic S, Jovanovic P et al.: Primary mucosal melanomas: a comprehensive review. Int J Clin Exp Pathol 2012; 5: 739–753.
4. Karimkhani C, Gonzalez R, Dellavalle RP: A review of novel therapies for melanoma. Am J Clin Dermatol 2014; 15: 323–337.
5. Gangadhar TC, Vonderheide RH: Mitigating the toxic effects of anticancer immunotherapy. Nat Rev Clin Oncol 2014; 11: 91–99.
6. Indini A, Guardo LD, Cimminiello C et al.: Investigating the role of immunotherapy in advanced/recurrent female genital tract melanoma: a preliminary experience. J Gynecol Oncol 2019; 30: e94.
7. Zhou S, Khanal S, Zhang H: Risk of immune-related adverse events associated with ipilimumab-plus-nivolumab and nivolumab therapy in cancer patients. Ther Clin Risk Manag 2019; 15: 211–221.

8. Baettig F, Vlajnic T, Vetter M et al.: Nivolumab in chemotherapy-resistant cervical cancer: report of a vulvitis as a novel immune-related adverse event and molecular analysis of a persistent complete response. J Immunother Cancer 2019; 7: 281.

9. Nagai H, Muto M: Optimal management of immune-related adverse events resulting from treatment with immune checkpoint inhibitors: a review and update. Int J Clin Oncol 2018; 23: 410–420.

10. Solinas C, Porcu M, De Silva P et al.: Cancer immunotherapy-associated hypophysitis. Semin Oncol 2018; 45: 181–186.

11. Weber JC, Kähler KC, Hauschild A: Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012; 30: 2691–2697.

12. Norwood TG, Wang MJ, Huh WK: Combination checkpoint inhibitor therapy induces multiple immune major related adverse events in the treatment of vaginal melanoma: a cautionary case report. Gynecol Oncol Rep 2019; 30: 100508.

13. Shrivastava SBL, Agrawal G, Mittal M et al.: Management of vaginal cancer. Rev Recent Clin Trials 2015; 10: 289–297.

14. Martinez-Castro P, Poveda A, Guinot JL et al.: Treatment of inoperable vulvar cancer: where we come from and where are we going. Int J Gynecol Cancer 2016; 26: 1694–1698.

15. Woelber L, Trillsch F, Kock L et al.: Management of patients with vulvar cancer: a perspective review according to tumour stage. Ther Adv Med Oncol 2013; 5: 183–192.

16. Courtney-Brooks M, Sukumvanich P, Beriwal S et al.: Does the number of nodes removed impact survival in vulvar cancer patients with node-negative disease. Gynecol Oncol 2010; 117: 308–311.

17. Horowitz NS, Olawaiye AB, Borger DR et al.: Phase II trial of erlotinib in women with squamous cell carcinoma of the vulva. Gynecol Oncol 2012; 127: 141–146.

18. Pleunis N, Schuurman MS, Van Rossum MM et al.: Rare vulvar malignancies; incidence, treatment and survival in the Netherlands. Gynecol Oncol 2016; 142: 440-445.

19. Lattanzi M, Lee Y, Simpson D et al.: Primary melanoma histologic subtype: impact on survival and response to therapy. J Natl Cancer Inst 2019; 111: 180–188.

20. Harris SJ, Brown J, Lopez J et al.: Immuno-oncology combinations: raising the tail of the survival curve. Cancer Biol Med 2016; 13: 171–193.

DOI: 10.15557/CGO.2020.0008 CURR GYNECOL ONCOL 2020, 18 (2), p. e39–e42