Clinical Characteristics and Treatment Response With Checkpoint Inhibitors in Malignant Melanoma of the Vulva and Vagina

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Genital tract melanomas are commonly categorized as mucosal melanomas, but this has been questioned by studies showing different mutational characteristics suggesting that vulvovaginal melanomas (VVMs) may be classified as a unique subclass.3–5 Data on VVMs are scarce, and to date, only 1 prospective study has been completed: The Gynecologic Oncology Group (GOG) 73 protocol suggested that the American Joint Committee on Cancer (AJCC) staging was the best predictor for survival and Breslow’s depth of invasion in lymphovascular space invasion were predictive of lymph node metastases.6 In a population-based study, we have recently shown that VVMs have a particularly poor prognosis with a median overall survival of 53 months in vulvar melanoma and 16 months in vaginal melanoma with no important change in survival over time.1

The treatment landscape of advanced and metastatic melanoma has drastically changed with the introduction of immune checkpoint inhibitors. Trials with the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor ipilimumab and the programmed cell death protein 1 (PD-1) inhibitors nivolumab and pembrolizumab have shown profound improvements of survival in patients with unresectable or metastatic melanoma.7–9 In a pooled analyses of clinical trials, mucosal melanomas, however, had lower response rates to nivolumab and pembrolizumab compared with cutaneous melanomas.10,11 Data for VVMs are scarce.

The aims of this study are to describe clinical characteristics of a comprehensive cohort of women with VVM treated at our institution and to assess the treatment response of immune checkpoint inhibitors in this patient cohort.

METHODS

Study Population

This is a retrospective single-center cohort study of women with invasive melanoma of the vulva or vagina treated at the Princess Margaret Cancer Centre in Toronto, Ontario, Canada. The study protocol was approved by the institutional review ethics board (UHN 19-5620). All women with histologically confirmed invasive vulvar or vaginal melanoma diagnosed over a period of 15 years (2004–2018) were included and all cases were reviewed by an expert pathologist at the time of initial presentation; women with melanoma in situ without invasive components were not included. Vulvar melanomas were staged according to the AJCC staging classification in the eighth edition, and vaginal melanomas were classified as local, regional, or distant.12 Demographic data, Eastern Cooperative Oncology Group performance (ECOG) score, histopathology, type of surgery, lymph node assessment, adjuvant treatment, recurrence, treatment details for recurrent disease, and vital status were extracted from the electronic patient records. Programmed death-ligand 1 was not routinely tested in our patient cohort. Selection for immunotherapy was based on availability. Treatment response was evaluated retrospectively using the “response criteria for use in trials testing immunotherapeutics”
The objective response rate (ORR) was defined as the proportion of patients with complete (iCR) or partial response (iPR) based on the best overall response (iBOR). The clinical benefit rate (CBR) was defined as the proportion of patients with iCR, iPR, or stable disease (iSD). An iSD was assigned if no disease progression occurred for at least 2 months. Adverse events were categorized using the common terminology criteria for adverse events version 5.0. The treatment response of immune checkpoint inhibitors was analyzed in our cohort. In addition, treatment response from previously published case series and case reports was identified from PubMed using the search terms “ipilimumab,” “nivolumab,” or “pembrolizumab” in combination with “vulva” or “vagina,” and a separate analysis was performed for our cohort and the combined cohort. Reports without information on treatment response were not included.

**Statistical Analyses**

Descriptive statistics was used to report demographic data. Continuous variables were compared using the Student t test, Mann-Whitney test, or Wilcoxon test, as appropriate. Categorical data were compared using the Fisher exact test. Progression-free survival (PFS) and overall survival (OS) for the comprehensive cohort were calculated from the date of diagnosis to date of progression or death (PFS) and date of diagnosis to date of death (OS). Progression-free survival and OS for the subgroup analysis of immune checkpoint inhibitors were calculated from the date of treatment initiation to the date of progression or death, respectively. The Kaplan-Meier method with log-rank test was used to analyze PFS and OS. The 2- and 5-year survival rates were calculated using the Kaplan-Meier method. Statistical analysis was performed using SPSS Version 26, IBM, Armonk. A p value of less than .05 was considered statistically significant, all tests were 2-sided.

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**RESULTS**

**Patient Characteristics**

In total, 32 women with invasive vulvar (n = 28) and vaginal (n = 4) melanoma were treated at our institution over a period of 15 years and included in our study. Demographic and clinical characteristics are shown in Table 1. The mean age at diagnosis was 66 years, and a significant proportion of patients was diagnosed with advanced disease stage, tumor thickness of greater than 4 mm, ulcerations, and high mitotic count; 31.3% already reported symptoms from melanoma including bleeding, pruritus, and pain at the time of diagnosis. Histologic characteristics are shown in Table 2. BRAF was tested in 25 patients and was

| TABLE 1. Patient Characteristics |
| Parameter | |
| Age at diagnosis, y | Mean ± SD 66.3 ± 14.0 |
| | Median (range) 66.0 (40–96) |
| Pregnancy history | Gravida 2 (0–3) |
| | Para 2 (0–3) |
| ECOG performance status at diagnosis | ECOG 0 23 (71.9%) |
| | ECOG 1 6 (18.8%) |
| | ECOG 2 2 (6.3%) |
| | ECOG 3 1 (3.1%) |
| History of previous malignancy | History of melanoma 2 (6.3%) |
| | History of other malignancy 7 (21.9%) |
| Tumor stage at diagnosis | Vulvar melanoma (n = 28) |
| | AJCC stage I 1 (3.6%) |
| | AJCC stage II 13 (46.4%) |
| | AJCC stage III 11 (39.3%) |
| | AJCC stage IV 3 (10.7%) |
| Vaginal melanoma (n = 4) | local 0 (0%) |
| | regional 4 (100%) |
| | distant 0 (0%) |
| Reported symptoms | Any symptoms reported 10 (31.3%) |
| | Pruritus 4 (12.5%) |
| | Bleeding 8 (25.0%) |
| | Pain 4 (12.5%) |
| Organ involvement | Labia majora 22 (68.8%) |
| | Labia minora 15 (46.9%) |
| | Clitoris 10 (31.1%) |
| | Urethra 4 (12.5%) |
| | Anus 0 (0%) |
| Surgery | Radical local excision 31 (96.9%) |
| | Exenteration 1 (3.1%) |
| Surgical lymph node assessment | Performed 27 (84.4%) |
| | Nodal metastases 14 (51.9%) |
| | Negative lymph nodes 13 (48.1%) |

(iRECIST). The objective response rate (ORR) was defined as the proportion of patients with complete (iCR) or partial response (iPR) based on the best overall response (iBOR). The clinical benefit rate (CBR) was defined as the proportion of patients with iCR, iPR, or stable disease (iSD). An iSD was assigned if no disease progression occurred for at least 2 months. Adverse events were categorized using the common terminology criteria for adverse events version 5.0. The treatment response of immune checkpoint inhibitors was analyzed in our cohort. In addition, treatment response from previously published case series and case reports was identified from PubMed using the search terms “ipilimumab,” “nivolumab,” or “pembrolizumab” in combination with “vulva” or “vagina,” and a separate analysis was performed for our cohort and the combined cohort. Reports without information on treatment response were not included.

| TABLE 2. Histologic Characteristics |
| Characteristics | |
| Tumor thickness, mm | Median (range) |
| ≤1.00 | 8 (1.1–68) |
| 1.01–2.00 | 0 (0%) |
| 2.01–4.00 | 4 (12.9%) |
| >4.00 | 7 (22.6%) |
| Uterincion | 20 (62.5%) |
| Mitotic count, mitoses/mm² | Median (range) |
| 0–50 | 8 (0–50) |
| 1 | 1 (3.4%) |
| 2–10 | 14 (48.3%) |
| >10 | 13 (44.8%) |
positive in 2 (8.0%), cKIT was positive in 3 (13.6%) of the 22 patients tested, and NRAS mutations were detected in 2 (13.3%) of the 15 patients tested. A mutation in SF3B1 was found in 2 patients and 1 woman was found to have a PTEN mutation.

All women underwent surgery, and the lymph node status was surgically evaluated in 84.4% of all patients and in 88.0% of those with nonmetastatic vulvar melanoma. Adjuvant systemic treatment was given in 5 patients (15.6%): adjuvant interferon α in 3 and nivolumab in 2 patients, and their outcome is reported hereinafter.

Outcome

At a median follow-up of 37.8 months (5.8–110.4), 26 (81.3%) women had disease progression and 16 (50%) died. The median PFS was 17.7 months (95% CI = 5.5–29.8 months), and the 2- and 5-year PFS rates were 35.4% and 23.2%, respectively. The median OS was 59.1 months (95% CI = 23.6–94.5 months), and the 2- and 5-year OS rates were 71.1% and 45.6%, respectively. The 2-year PFS rate by the AJCC stage in vulvar melanoma was as follows: stage I, 100%; stage II, 35.9%; stage III, 42.4%; stage IV, 33.3%; and in the 4 patients with regional vaginal melanoma, 0% (p = .126).

Fifteen (51.7%) of the 29 nonmetastatic patients at diagnosis developed distant metastases with a median time to metastatic disease of 39.5 months (95% CI = 0–84.2 months). Two patients received adjuvant nivolumab: 1 patient with vaginal melanoma developed brain metastases during adjuvant treatment with nivolumab. She was treated with stereotactic radiation and switched to pembrolizumab. The best overall response was isSD, but she ultimately progressed and died of melanoma (see Table 3, PMH05). The second patient receiving adjuvant nivolumab had vulvar melanoma AJCC stage IIIC. She had a local recurrence after 77 months, which was excised, and she has now been recurrence-free for 8 months.

Treatment Response of Immune Checkpoint Inhibitors in Unresectable or Metastatic Melanoma

Thirteen patients with locally unresectable or metastatic melanoma were treated with immune checkpoint inhibitors, and 4 patients were initially treated with ipilimumab and switched to a PD-1 inhibitor after treatment failure. The best overall ORR with immunotherapy in the 13 patients was 30.8% (95% CI = 5.7%–55.9%), and the CBR was 61.5% (95% CI = 35.1%–88.0%). The median PFS was 4.0 months (95% CI = 2.3–5.7 months), and the median OS was 17.0 months (95% CI = 12.7–21.3 months). Ipilimumab was given in 8 patients; the ORR was 12.5% (95% CI = 0%–35.4%), and the CBR was 25.0% (95% CI = 0%–55.0%). Programmed cell death protein 1 inhibitors or a combination of CTLA-4 and PD-1 inhibitors were given in 9 patients; the ORR was 33.3% (95% CI = 2.5%–64.1%), and the CBR was 66.7% (95% CI = 35.9%–97.5%).

In addition, 13 patients with VVM receiving immune checkpoint point inhibitors were identified from previously published cases in the literature.15–20; 10 patients with metastatic or unresectable VVM were included (see Table 3); 3 patients, who received neo-adjuvant ipilimumab and radiation and subsequently underwent surgery, were not included.20 The best overall ORR with immune checkpoint inhibitors in the combined cohort of the 23 patients was 30.4% (95% CI = 11.6%–49.2%), and the CBR was 52.2% (95% CI = 31.8%–72.6%). The median PFS was 4.0 months (95% CI = 2.7–5.3 months), and the median OS was 17.0 months (95% CI = 12.7–21.3 months). The ORR for ipilimumab alone was 8.3% (95% CI = 0%–24%) compared with 37.5% (95% CI = 13.8%–61.2%, Fisher exact, p = .184) for PD-1 inhibitors or a combination of CTLA-4 and PD-1 inhibitors. The CBR was 16.7% (95% CI = 0%–37.8%) for ipilimumab compared with 62.5% (95% CI = 38.8%–86.2%, Fisher exact, p = .023) for PD-1 inhibitors or a combination of CTLA-4 and PD-1 inhibitors. The median PFS for ipilimumab alone was 3.0 months (95% CI = 2.6–3.4 months) compared with 9.0 months (95% CI = 1.9–16.1 months, p = .062) for PD-1 inhibitors or the combination of CTLA-4 and PD-1 inhibitors. Severe adverse events (grade 3/4) were observed in 2 (15.4%) of the 13 patients in our cohort and 3 (13.0%) of the 23 patients in the total cohort.

DISCUSSION

In this study, we report the clinical characteristics of VVM and the treatment response to immune checkpoint inhibitors in a comprehensive cohort.

Most women were diagnosed in advanced disease stages with poor prognostic indicators. Half of the nonmetastatic patients undergoing surgical lymph node assessment had lymph node metastases, and most our patients had a high mitotic count, both of which were recently shown to be important independent predictors for survival in women with VVMs.1–21 More than 50% of our cohort had disease recurrence or progression with a 2- and 5-year PFS rate of 35.4% and 23.2%, respectively. More than 50% of the women, who were free of distant metastases at diagnosis, developed metastatic disease. Therefore, women with VVM represent a high-risk group.

Consistent with previous reports and unlike in cutaneous melanomas, only a small proportion of patients had BRAF mutations, limiting the treatment options with BRAF/MEK inhibitors.3,4 cKIT mutations were observed 14% and NRAS mutations in 13%; 2 patients were found to have a mutation in SF3B1, a mutation that was recently found to be more prevalent in VVMs and may be associated with worse outcome.22–25

The introduction of immune checkpoint inhibitors has led to an enormous progress in melanoma treatment and checkpoint inhibitors are now United States Food and Drug Administration and European Medicines Agency approved in the adjuvant and metastatic setting. The mechanism of action of CTLA-4 and PD-1 inhibitors is shown in Figure 1. For ipilimumab, we have observed an ORR of 8.3% and a CBR of 16.7% with median PFS of 3.0 months. The ORR is notably lower compared with 21.2% in cutaneous melanoma but identical to the recently reported response rate in mucosal melanomas combining data from 6 clinical trials (2 phase I trials: CA209-00323 and CA209-03824; 1 phase II trial: CheckMate 06925; and 3 phase III trials: CheckMate 06626, CheckMate 03727, and CheckMate 06728,10).

For PD-1 or a combination of PD-1 and CTLA-4 inhibitors, the ORR was 37.5% and the CBR was 62.5% with a median PFS of 9.0 months. This is again lower compared with the ORR of 60.4% reported for a combination of nivolumab and ipilimumab10 but comparable with 40.9% for nivolumab28 and 33.0% for pembrolizumab (combining 3 clinical trials, KEYNOTE-001,28 KEYNOTE-002,29 and KEYNOTE-00631 in cutaneous melanoma). Severe adverse events were observed in 15.4% of our cohort, which is comparable with the rate observed in mucosal melanomas.30

Strengths and Limitations

This study investigates a large series of well-described cases of vulvar and vaginal melanoma diagnosed and treated at a comprehensive cancer center. We report clinical characteristics, outcome and treatment response with immune checkpoint inhibitors. The study is, however, limited by its retrospective design. Furthermore, including case reports into the analysis of treatment response adds the risk of publication bias. We have therefore analyzed our own series including all patients with VVM treated at our institution separately, and no distortion of
| Patient | Site | Stage at treatment initiationa (metastases) | Prior systemic therapy | Prior XRT, Site | Immunotherapy | iBOR | PFSb | irAEs | OSc | Vital status |
|---------|------|-----------------------------------------|----------------------|----------------|----------------|------|------|-------|------|--------------|
| PMH01   | Vulva | IIIIC, unresectable                      | None                 | None           | Pembrolizumab  | iCPD | 2    | None  | 18   | Alive with disease |
| PMH02   | Vulva | IV (lung)                                | None                 | None           | Ipilimumab + nivolumab | iSD | 18   | Uveitis G1, peripheral sensory neuropathy G3 | 18 | Alive with disease |
| PMH03   | Vulva | IV (liver)                                | None                 | None           | Ipilimumab + nivolumab | iCPD | 1    | None  | 1    | Died of disease |
| PMH04   | Vulva | IV (liver)                                | None                 | None           | Pembrolizumab  | iSD | 4    | None  | 16   | Died of disease |
| PMH05   | Vagina | Distant (brain)                          | Nivolumab, adjuvant | None           | Pembrolizumab  | iSD | 56   | None  | 56   | Alive with NED |
| PMH06   | Vulva | IV (lung)                                | Interferon, adjuvant | None           | Ipilimumab     | iCPD | 3    | Maculopapular exanthema G1, Hepatitis G1 | 17 | Died of disease |
| PMH07   | Vulva | IV (lung, liver)                         | None                 | None           | Pembrolizumab  | iSD | 4    | None  | 4    | Died of disease |
| PMH08   | Vulva | IV (liver)                                | None                 | Liver          | Ipilimumab     | iCPD | 3    | Maculopapular exanthema G1 | 50 | Alive with disease |
| PMH09   | Vulva | IV (lung, brain)                         | Carboplatin/paclitaxel | Brain         | Ipilimumab     | iCPD | 3    | None  | 6    | Died of disease |
| PMH10   | Vulva | IV (lung)                                | Dacarbazone          | Groin          | Ipilimumab     | iCPD | 3    | None  | 87   | Alive with NED |
| PMH11   | Vulva | IV (lung, bone)                          | None                 | Vulva + groin  | Ipilimumab     | iCPD | 1    | None  | 1    | Died of disease |
| PMH12   | Vulva | IV (lung, abdomen)                       | Carboplatin/paclitaxel | Abdomen + groin | Ipilimumab     | iCPD | 3    | None  | 16   | Died of disease |
| PMH13   | Vulva | IV (lung, abdomen, soft tissue)          | Carboplatin/paclitaxel | Abdomen + groin | Ipilimumab     | iSD | 2    | None  | 13   | Died of disease |
| Indini1  | Vulva | IV (lung)                                | CVD                  | None           | Ipilimumab     | iCPD | 4    | None  | 7    | Died of disease |
| Indini2  | Vulva | IV (lung, bone)                          | None                 | None           | Pembrolizumab  | iPR | 10   | Arthralgia G2, hypothyroidism G2 | 10 | Alive with disease |
| Indini3  | Vagina | Distant (liver)                         | None                 | None           | Pembrolizumab  | iCPD | 2    | None  | 4    | Alive with disease |
| Indini4  | Vagina | Distant (n.s.)                           | None                 | Vagina         | Nivolumab      | iSD | 4    | Cutaneous rash G1 | 4 | Alive with disease |
| Indini5  | Vagina | Distant (liver, pancreas, soft tissues, bone) | None                 | None           | Ipilimumab     | iCPD | 3    | None  | 7    | Died of disease |
| Indini6  | Vagina | Distant (lung)                           | Dacarbazone          | None           | Ipilimumab     | iCPD | 3    | None  | 18   | Died of disease |
| Daix1    | Vagina | Regional, unresectable                   | None                 | None           | Nivolumab      | iCR | 8    | Pruritus G1 | 8 | Alive with NED |
| Anko1   | Vagina | Distant (lung, liver, bone)              | None                 | None           | Nivolumab      | iPR/iCR | 17 | Thyroiditis, n.s. | 17 | Alive |
| Komatsu-Fujii1 | Vagina | Distant (lung)                          | None                 | None           | 1. Nivolumab    | iCPD | n.s. | n.s.  | n.s. | Alive with disease |
|         |      |                                          |                      | None           | 2. Pembrolizumab | iCPD | n.s. | n.s.  | n.s. | Alive with disease |
|         |      |                                          |                      | None           | 3. Ipilimumab   | iCPD | n.s. | n.s.  | n.s. | Alive with disease |
| Inoue1  | Vagina | Distant (brain)                          | None                 | Brain          | Nivolumab      | iCPD | 2    | Hepatitis G3 | n.s. | Alive with disease |

Characteristics of the 13 patients treated at our institution (PMH1–PMH13) and 10 additional previously published cases.

aStage at initiation of treatment with immune checkpoint inhibitor, AJCC stage for vulvar melanomas and local/regional/distant for vaginal melanomas.
bPFS in months defined from treatment initiation with immune checkpoint inhibitor to date of progression or death.
cOS in months defined from treatment initiation with first immune checkpoint inhibitor to date of last follow-up or death.

CVD indicates cisplatin-vinblastine-dacarbazone; DM, diabetes mellitus; G, grade; iCPD, confirmed progressive disease; irAEs, immune-related adverse events; NED, no evidence of disease; n.s., not specified; XRT, radiation therapy.
higher CBR and a trend toward longer progression-free survival. CTLA-4 and PD-1 inhibitors were associated with a significantly one third of women with locally unresectable or metastatic VVM. A complete or partial response being observed in approximately overall prognosis. Immune checkpoint inhibitors are effective with cases previously published in the literature. the response rates was observed when adding the additional 10 CONCLUSIONS Women with VVM constitute a high-risk group with poor overall prognosis. Immune checkpoint inhibitors are effective with a complete or partial response being observed in approximately one third of women with locally unresectable or metastatic VVM. Programmed cell death protein 1 inhibitors or a combination of CTLA-4 and PD-1 inhibitors were associated with a significantly higher CBR and a trend toward longer progression-free survival compared with CTLA-4 inhibitors alone.

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