Editorial Commentary

Immunotherapy for mucosal melanoma

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Introduction

Mucosal melanoma is a rare subtype, representing 1% of all melanoma diagnoses (1). As compared to cutaneous melanoma, patients with mucosal melanoma often present with more advanced disease and prognosis is significantly worse (2).

Given the rarity of the diagnosis, there has only been one prospective clinical trial enrolling solely patients with mucosal melanoma. The majority of data comes from subset analyses of patients with mucosal melanoma enrolled in general melanoma trials.

Mucosal melanoma has been shown to be significantly different from cutaneous melanoma with regard to its pathogenesis and epidemiologic/clinical characteristics. As such, it is important to evaluate these patients as a separate subset in order to give patients realistic expectations for their disease course.

In this study the authors present data on the efficacy and safety of pembrolizumab in patients with advanced mucosal melanoma treated on KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006.

Current study

The KEYNOTE 001, 002 and 006 trials were designed to evaluate the efficacy and safety of pembrolizumab alone (KEYNOTE 001), pembrolizumab compared to chemotherapy (KEYNOTE 002), or pembrolizumab compared to immunotherapy with ipilimumab (KEYNOTE-006). In total, 1,567 patients were treated on the aforementioned trials of which 84 (5%) of patients had mucosal melanoma.

The baseline characteristics of mucosal and cutaneous melanoma patients were comparable, with the exception of BRAF mutation status, which is known to be of lower frequency in patients with mucosal melanoma. In patients with mucosal melanoma treated with pembrolizumab, the objective response rate (ORR) was 19% (compared to 33% in patients with a cutaneous primary). In responders, the median durability of response was similar between mucosal and cutaneous primaries with 75% and 72% having an ongoing response, respectively. The median overall survival was significantly shorter for patients with mucosal melanoma (11.3 months) as compared to patients with a cutaneous primary (23.5 months). From a safety standpoint, rates of grade 3/4 treatment related adverse events were lower in mucosal patients (10%) than in patients with a cutaneous primary (18%).

Limitations

The study provides important information on efficacy and safety of pembrolizumab in patients with advanced mucosal melanoma. A breakdown of response rates by primary site (head/neck, anorectal, gynecologic) would be of interest to determine if a response was more or less likely based on the location of the primary tumor. Twenty-one percent of the mucosal melanoma patients in the study had prior chemotherapy. It is unknown if this chemotherapy was given in the adjuvant or metastatic setting. It may have been helpful to breakdown response by PD-L1 positivity as PD-L1 positive patients were found to have higher

response rates in a similar subset analysis performed on mucosal melanoma patients treated with nivolumab (3). A subsequent analysis with updated information on durability of response would also be of interest as 75% of the patients had responses ongoing at the time of data cut-off. Finally, additional information regarding country of origin would be important to know given the significantly higher incidence of mucosal melanoma in Asia as compared to Western countries.

Discussion

While cutaneous and mucosal melanoma both originate from melanocytes, they differ significantly in their pathogenesis and epidemiologic/clinical characteristics. Classic risk factors for cutaneous melanoma such as: sun exposure, family history of melanoma, nevus count and racial background (4) have not been shown to play a role in the pathogenesis of mucosal melanoma.

From an epidemiologic standpoint, there are significant racial differences in the prevalence of mucosal melanoma. In non-Hispanic whites, mucosal melanomas are rare, representing ~1% of all melanoma diagnoses. In contrast, 9% of melanomas diagnosed in blacks and 15% of melanomas diagnosed in Asians in the US are mucosal primaries (5). In China, mucosal melanomas represent 23% of all melanoma diagnoses (6).

Mucosal melanomas are often classified by primary site into three main categories: head/neck, vulvovaginal and gastrointestinal with incidence split roughly evenly among these categories [26–38% head/neck, 22–35% vulvovaginal and 30–38% gastrointestinal (7,8)]. A Chinese study of >700 patients with mucosal melanoma evaluated location of metastatic disease by primary site and found that locations of metastases were similar amongst primary sites. The only exception was that mucosal melanomas of the oral cavity had a higher incidence of lung only metastases as compared to other sites (32.5 *vs.* 18.5%, P=0.007). Given this, they concluded that the mutational events resulting in metastases in mucosal melanoma are independent of anatomic site of origin and that therapies can be applied equally, regardless of primary site (7). In this study the 5-year overall survival was not significantly different by primary site with a 5-year OS of 27% in head/neck primary, 16% in gastrointestinal primary and 20% in gynecologic/urologic primaries.

Whereas most patients with cutaneous melanoma presents with early, localized disease, with only 9% of patients having locoregional lymph node involvement at diagnosis, mucosal melanoma is often diagnosed at a later stage with frequent rates of lymph node involvement (21% head/neck, 61% anorectal, 23% vulvovaginal) (2) and distant metastatic disease (23%) on presentation (7). Even in patients presenting with localized disease, definitive surgical management of the primary is more difficult than for patients with cutaneous primaries. Patients with mucosal melanoma often suffer from a "field effect" [frequent development of multiple primaries in nearby tissue (4)] precluding clear margins.

These differences in risk factors and clinical behavior may be related to differences at the molecular level. While BRAF is a common mutation found in cutaneous melanoma, seen in ~50% of cases (9), it is found in only is 8–12% in patients with mucosal melanoma (7,8,10). KIT mutations may be more common than in cutaneous melanoma and are seen in 8–25% of mucosal melanomas (7).

In general, cutaneous melanoma is not felt to be a disease that is significantly responsive to chemotherapy and studies of adjuvant chemotherapy have not shown a benefit in survival (11). While studies of chemotherapy for mucosal melanoma are sparse, a prospective randomized phase 2 trial demonstrated prolonged overall survival in patients treated with adjuvant cisplatin + temozolomide as compared to observation for patients with resected mucosal melanoma in China (12).

An analysis similar to that presented by Hamid *et al.* was performed by D'Angelo *et al.* for patients with mucosal melanoma treated with nivolumab alone, or in combination with ipilimumab (3). In total 1,112 patients received nivolumab alone or in combination with ipilimumab. Eleven percent (121 patients) had mucosal melanoma. Outcomes were similar to that seen with pembrolizumab with an ORR 23% for nivolumab monotherapy. Of the 35 patients with a mucosal primary who received combination therapy with ipilimumab and nivolumab, the ORR was 37% (as compared to 60% in patients with a cutaneous primary).

In this analysis the authors evaluated response by PD-L1 status. In patients treated on these studies, PD-L1 positive was defined as ≥5% of the tumor cells exhibiting cell surface PD-L1 staining of any intensity in a section containing at least 100 tumor cells. Of note, the "PD-L1 positive" definition is different in the pembrolizumab studies where PD-L1 positive is defined as PD-L1 staining in at least 1% of tumor cells. Relative to cutaneous melanoma, a lower percentage of mucosal melanoma patients were PD-L1 positive (17.4% *vs.* 34.3 % for nivolumab monotherapy

and 28.6% *vs.* 36.8% for combination ipilimumab + nivolumab). In PD-L1 positive mucosal melanoma patients treated with nivolumab (15 patients) the ORR was 53.3% [as compared to 12.2% in PD-L1 negative patients (49 patients)]. In PD-L1 positive mucosal melanoma patients treated with ipilimumab + nivolumab (10 patients), the ORR was 60% [as compared to 33% in PD-L1 negative patients (18 patients)]. The magnitude of difference in response rate between PD-L1 positive and negative patients treated with nivolumab was larger in the mucosal subset than the cutaneous patients (PD-L1 + cutaneous 55.7% *vs.* 35% in PD-L1 negative patients). When evaluating all patients, response rates to nivolumab were lower in mucosal primary compared to cutaneous (23% *vs.* 40.9%), however when looking at just the subset of PD-L1 positive patients, response rates were similar (53.3% mucosal primary *vs.* 55% cutaneous primary). While PD-L1 is not typically used as a biomarker for treatment selection in cutaneous melanoma, this difference in response rates may warrant further investigation in mucosal melanoma.

The mucosal melanoma responses rates shown in this subset analysis are comparable to non-melanoma cancer response rates to immunotherapy [bladder cancer 21% (13), head neck 13% (14), lung cancer (PD-L1 >1%) 18% (15)]. While a "biomarker" predicting response to immunotherapy has yet to be found, tumor mutational burden is frequently cited as a predictor of response to immunotherapy. As compared to other cancers, cutaneous melanoma has a high average tumor mutational burden of 13 mutations/megabase (16). In contrast, mucosal melanoma has a tumor mutational burden of 2 mutations/megabase, similar to that of a less immunologically active cancer such as breast cancer (17).

Conclusions

Similar to patients with cutaneous primaries, patients with advanced, unresectable mucosal melanoma should be treated with front line immunotherapy. Providers should be aware that response rates are lower than those seen in patients with a cutaneous primary, but some patients can achieve durable and long-lasting responses.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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