Prognostic value of BRAF mutations in localized cutaneous melanoma

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Background: BRAF mutations are frequent in melanoma but their prognostic significance remains unclear.

Objective: We sought to further evaluate the prognostic value of BRAF mutations in localized cutaneous melanoma.

Methods: We undertook an observational retrospective study of 147 patients with localized invasive (stages I and II) cutaneous melanomas to determine the prognostic value of *BRAF* mutation status.

Results: After a median follow-up of 48 months, patients with localized melanomas with *BRAF*-mutant melanomas exhibited poorer disease-free survival than those with *BRAF*-wt genotype (hazard ratio 2.2, 95% confidence interval 1.1-4.3) even after adjustment for Breslow thickness, tumor ulceration, location, age, sex, and tumor mitotic rate.

Limitations: The retrospective design and the small number of events are limitations.

Conclusions: Our findings suggest that reappraisal of clinical treatment approaches for patients with localized melanoma harboring tumors with BRAF mutation might be warranted. (J Am Acad Dermatol 2014;70:858-62.)

Key words: BRAF; localized; melanoma; NRAS; prognosis; survival.

Despite recent advances in therapy, particularly the introduction of inhibitors of defined molecular targets, the prognosis for metastatic melanoma remains poor. In the last few years, an emerging new classification for melanoma based on mutation profile has been suggested, with BRAF, NRAS, and KIT alterations currently considered the most relevant.[1,2]

BRAF mutations are found in roughly 40% of cutaneous melanomas and the development of specific BRAF inhibitors has increased the importance of their detection.[3] BRAF mutations are associated with younger age at diagnosis, less solar elastosis, higher total body nevus counts, and some specific histopathologic findings (heavy melanization, prominent upward epidermal scatter of melanocytes, nest formation of intraepidermal melanocytes, and ulceration).[4-8] In addition, BRAF-mutated melanomas usually present as more advanced-stage lesions, are frequently ulcerated,

Abbreviations used:

DFS: disease-free survival
OS: overall survival

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Conflicts of interest: None declared.

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and have higher tumor mitotic rates compared with wild-type tumors.[6,9-11] Despite in vitro data suggesting enhanced oncogenic effects, the presence of BRAF mutation as an independent prognostic factor for survival has not been conclusively shown.[6,9-13]

Potentially, if BRAF mutations were independently related to poorer prognosis, this might support the administration of adjuvant therapy, for example, a BRAF inhibitor. This study aimed to further evaluate the prognostic value of BRAF mutations in localized cutaneous melanoma at a single institution. In addition, we explored whether mutations in NRAS also had prognostic significance, independently of BRAF.

CAPSULE SUMMARY

- Melanoma is responsible for the majority of deaths from skin cancer and despite recent advances in therapy the prognosis for some patients remains poor.
- This study confirms *BRAF* mutation as an indicator of poor prognosis in patients with localized melanoma.
- Reappraisal of clinical treatment approaches for this group of patients may be warranted.

METHODS

An observational retrospective study included patients with localized invasive cutaneous melanomas registered between January 1, 2004, and May 31, 2012, in the database of the Dermatology Department of the Instituto Valenciano de Oncología. This database includes all cases collected consecutively since January 2000 and definitively treated at that institution, the characteristics of which are described in detail in previous studies.[14,15] Maintenance of the database includes daily update of patient follow-up. This study was approved by our institutional review board.

Patients whose initial presentation was with metastatic melanoma or those with multiple primary invasive melanomas were not included. Only patients with melanomas located on extremities or the trunk were selected. Rare subtypes of melanoma including acral lentiginous melanomas and Spitzoid or nevoid lesions were excluded because they appear to have different origins and behavior from the more prevalent forms of cutaneous melanoma. Eligible patients were included in the study only if sufficient DNA from the primary tumor was available for mutation analysis. BRAF V600 and NRAS Q61 mutations were detected after the methods previously described.[16]

The main variable was defined as the presence of BRAF or NRAS mutation. We considered the 3 groups defined by the presence of mutated NRAS, mutated BRAF, or wild type for both genes. Also, as our main goal was to evaluate the impact of BRAF mutation in survival, we further divided the studied population into 2 groups according to the presence or absence of mutation in BRAF.

For the purpose of this study the following variables were also retrieved from the melanoma database: age, sex, location (trunk vs extremities), Breslow thickness (≤ 2.00 vs >2.00 mm), ulceration (presence vs absence), and tumor mitotic rate (≤ 5 vs >5 mit/mm^2). These variables were selected because they have all been demonstrated to have an impact on survival in large series and, accordingly, they were used in the multivariate analyses.

The primary end points of this study were overall survival (OS) and disease-free survival (DFS). To avoid the influence of BRAF inhibitors on OS in patients who developed metastasis and were treated with vemurafenib, the follow-up was censored for those cases at the date of initiation of the therapy. Differences in survival probabilities were calculated by the Kaplan-Meier method and evaluated by the log rank test. Multivariate analyses for prognostic factors were based on the Cox proportional hazards model. The "enter" method was used to adjust for all selected variables. For all tests a P value no greater than .05 was considered statistically significant. All analyses were carried out with a software package (SPSS Statistic 15.0, IBM Corp, Armonk, NY).

RESULTS

The age, sex, tumor thickness, and ulceration distribution of the 147 patients who were genotyped did not differ from the 728 patients who were not genotyped (Supplementary Table I; available at http://www.jaad.org). The median age was 53 years (interquartile range, 42-66 years), and 68 were men (46.3%). Most tumors presented on axial location (n = 92, 62.6%). Tumors had a median thickness of 1.00 mm (interquartile range, 0.60-2.00 mm) and 26 (17.7%) were ulcerated. The distribution of histologic types included superficial spreading 75.5%, nodular 17.7%, lentigo malignant 2.7%, and other/unclassified 4.1%. The median follow-up period was 49 months (4.08 years).

A total of 38 (25.9%) patients with mutated BRAF and 27 (18.4%) with mutated NRAS, who were mutually exclusive, were identified. Of BRAF-mutant cases, 29 (76%) harbored V600E, 7 (19%) V600K, and 2 (5%) V600D. Of NRAS-mutant cases, 13 (48%) had