Prognostic factors in distinct melanoma types

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CHAPTER 6

Sentinel node biopsy in cutaneous melanoma patients with germline *CDKN2A* mutations

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INTRODUCTION

Sentinel node biopsy (SNB) has become a routine staging procedure with prognostic and therapeutic impact in patients with cutaneous melanoma. Sentinel node status is the strongest prognostic factor for survival in clinically localized melanoma patients.[1] Approximately 10% of melanoma patients have a family history of this disease. Germline mutations in the *CDKN2A* gene, encoding the p16 and p14 tumor suppressor proteins, are the most common cause of familial melanoma.[2] These patients with familial atypical multiple mole melanoma (FAMMM) syndrome have a life-time melanoma risk of approximately 70%.[2,3] Melanoma-specific survival of patients with germline *CDKN2A* mutations has been reported to be worse than of patients with sporadic melanoma.[3] Since the biology of melanoma in *CDKN2A* mutation carriers appears to be more aggressive, we hypothesized that the frequency and predictive value of sentinel node-positivity might be different in this patient group. This study reports the characteristics and outcomes of patients with hereditary melanoma carrying germline *CDKN2A* mutations who underwent SNB.

METHODS

In this multicenter, retrospective case series, all CDKN2A mutation carriers with clinically-localized cutaneous melanoma who underwent SNB at 4 tertiary referral centers (Leiden University Medical Center, Leiden, the Netherlands; Melanoma Institute Australia, Sydney, Australia; Leeds Institute of Medical Research, Leeds, UK; and Karolinska Institutet, Stockholm, Sweden) between January 2000 and April 2015 were included. Demographics, tumor characteristics and follow-up data were collected.

RESULTS

SNB was performed in 23 melanoma patients carrying germline *CDKN2A* mutations. Fifteen patients were female and eight male; the median age was 47 years (range 20–70 years). Seven patients had previously been diagnosed with primary melanoma. Melanomas were located on the trunk in nine patients, lower limb in eight patients, upper limb in four patients, and two patients had their melanoma located in the head and neck region. The median Breslow-thickness was 1.5mm (range 0.8– 3.3mm), four melanomas were ulcerated, and 15 had a tumor mitotic rate $\geq 1/mm^2$. Lymphoscintigraphy showed drainage to a median of two sentinel nodes and five melanomas drained to multiple nodal regions. Sentinel node was

positive in five patients. Breslow-thickness of the sentinel node-positive melanomas ranged from 1.1 to 2.9 mm, one was ulcerated and all had tumor mitotic rate ≥1/mm^2. Completion lymph node dissection (CLND) was performed in three sentinel node-positive patients, while two patients declined the procedure. Only one patient who underwent CLND had metastasis in a non- sentinel node lymph node.

During a median follow-up time of 100 months, three patients experienced a locoregional recurrence and three patients developed systemic metastatic disease. At the end of this period, 17 patients were still alive, two patients had died of melanoma and three patients of other causes. Of the five sentinel node-positive patients, one had a local recurrence and another developed systemic metastases and died of melanoma. This female patient had been diagnosed with stage IIIA (pT2aN2a) melanoma on the trunk and survived for 3years. Two of the 17 sentinel node-negative patients (12%) developed a local recurrence and two had systemic metastases. One female patient with a stage IB (pT2aN0) melanoma on the left lower leg died 6 years later from her disease. Three patients, all sentinel node-negative, died of other causes.

DISCUSSION

This is the first study to present results from SNB in patients with hereditary melanoma due to germline *CDKN2A* mutations (FAMMM syndrome), whose melanomas have been reported to behave more aggressively.[3] The emergence of effective adjuvant systemic treatment in SN-positive patients and the recent report of superior immunotherapy responses in *CDKN2A* mutations carriers make SNB an even more important staging tool.[4,5] Although *CDKN2A* mutation carriers were reported to have worse survival than sporadic melanoma patients, we did not observe a higher sentinel node-positivity rate in our case series. The sentinel node-positivity rate of 22% in our study is not inconsistent with what has been reported for patients with sporadic intermediate-thickness melanomas.[1,3] As only two melanoma-related deaths occurred in this cohort we cannot draw reliable conclusions regarding the prognostic value of SNB. Genetic testing for a germline *CDKN2A* mutation is recommended in patients suspected of hereditary melanoma. In our clinics, we see these patients more regularly than patients without the mutation and advise screening for pancreatic cancer from the age of 40 years.

In our experience, there may be reluctance to perform SNB in this particular patient group. Since over 40% of *CDKN2A* mutation carriers have multiple primary melanomas, many of them would have been excluded from clinical trials investigating SNB.[1,3] Patients with multiple

primary melanomas probably often have multiple sentinel nodes and drainage to more than one basin. Although the procedure might be more extensive, having multiple melanomas is not a contraindication for SNB. Due to surveillance, melanomas are on average diagnosed at an earlier stage in *CDKN2A* mutation carriers than in sporadic melanoma patients, limiting the experience with SNB in this patient group.[3]

There are several limitations affecting this study of which the small size of the cohort is the most important one. Other limitations are the retrospective design and potential selection bias.

CONCLUSION

The sentinel node-positivity rate for patients with *CDKN2A* mutation and for patients with sporadic melanoma appears to be similar. There should be no reluctance to perform SNB in these patients.

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