MELANOMA AND MELANOCYTIC NAEVI

INTRA-PATIENT HETEROGENEITY OF BRAF, NRAS, C-KIT AND NF-1 MOLECULAR ALTERATIONS DURING MELANOMA PROGRESSION

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Introduction: Assessment of molecular subtypes, defined according to the presence of driver alterations in BRAF, NRAS, c-KIT and NF-1 genes, is of interest for patients with advanced melanoma, to ensure an accurate selection for target therapy.

Objective: We investigated the frequency and distribution of BRAF, NRAS, c-KIT and NF-1 molecular alterations in primary melanoma and related metastases and evaluated the intra-patient heterogeneity of mutational profiles during progression.

Materials and Methods: Seventy-two FFPE paired samples of primary melanomas and related nodal and/or visceral metastases from 31 patients were analyzed by molecular methods (for BRAF and NRAS, c-KIT mutations) using Real-Time PCR and Sanger Sequencing or by immunohistochemistry (for c-KIT and NF-1 genetic alterations) using the anti-human CD117/c-Kit polyclonal antibody and the clone McNFn27b, respectively.

Results: Overall, BRAFV600 mutations were observed in 45.8% of the samples (19.4% primaries; 26.4% metastasis), with 75% carrying the BRAFV600E mutation and 24.2% the BRAFV600K. NRASQ61 mutations were found in 22.2% (8.3% primaries; 13.9% metastasis), with 50% NRASQ61R, 43.7% NRASQ61L and 6.3% NRASQ61K. We detected the c-KITL802Fmutation in 1.4% of cases. According to IHC, c-KIT resulted overexpressed in 48.6% cases (25% primary; 23.6% metastasis), whereas NF1 expression was down-regulated in 1.4% samples. Intra-patient BRAF concordance between primary melanoma and related metastases was in 87.1% of patients, with 44.4% being concordant for the BRAFV600 mutation and 55.6% for wild-type genotype. A discrepant profile was detected in 12.9% patients and its occurrence was not associated with a specific location of metastases. Regarding intra-patient mutational profile concordance of all four genes, 45.2% of the patients showed a consistent pattern of BRAF/NRAS/c-KIT/NF-1 status between the

primary lesion and related metastases. Intra-patient discordance was present in 54.8% patients, mainly because differences in c-KIT amplification.

Conclusions: A clinically meaningful intra-patient heterogeneity exists between primary and metastatic lesions, supporting the polyclonal model of melanoma progression.