Prognostic relevance of $MLH1$ and $MSH2$ mutations in hereditary non-polyposis colorectal cancer patients

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ABSTRACT

Aims and background. Colorectal carcinoma patients from hereditary non-polyposis colorectal cancer families are suggested to have a better prognosis than sporadic colorectal carcinoma cases. Since the majority of hereditary non-polyposis colorectal cancer-related colorectal carcinomas are characterized by microsatellite instability due to germline mutations in DNA mismatch repair genes, this is consistent with the prolonged survival observed in sporadic microsatellite instability-positive colorectal carcinoma compared to microsatellite stable cases. However, a fraction of colorectal carcinoma cases belongs to families that, despite fulfilling the clinical criteria for hereditary non-polyposis colorectal cancer, do not carry mismatch repair gene mutations. Our aim was to verify to what extent the genotypic heterogeneity influences the prognosis of hereditary non-polyposis colorectal cancer patients.

Methods. A survival analysis was performed on 526 colorectal carcinoma cases from 204 Amsterdam Criteria-positive hereditary non-polyposis colorectal cancer families. Enrolled cases were classified as $MLH1$-positive, $MSH2$-positive and mutation-negative, according to the results of genetic testing in each family.

Results. Five-year survival rates were 0.73 (95% CI, 0.66-0.80), 0.75 (95% CI, 0.66-0.84) and 0.62 (95% CI, 0.55-0.68) for $MLH1$-positive, $MSH2$-positive and mutation-negative groups, respectively (logrank test, $P = 0.01$). Hazard ratio, computed using Cox regression analysis and adjusted for age, sex, tumor site and stage, was 0.71 (95% CI, 0.51-0.98) for the mutation-positive compared to the mutation-negative group. Moreover, in the latter group, patients with microsatellite instability-positive colorectal carcinomas showed a better outcome than microsatellite stable cases (5-year survival rates, 0.81 and 0.60, respectively; logrank test, $P = 0.006$).

Conclusions. Our results suggest that the prognosis of hereditary non-polyposis colorectal cancer-related colorectal carcinoma patients depends on the associated constitutional mismatch repair genotype.