To the editor:

The Ki67 proliferation index is a quantitative indicator of clinical risk in mantle cell lymphoma

Mantle cell lymphoma (MCL) is a distinctive type of non-Hodgkin lymphoma (NHL) that is considered an aggressive neoplasm. The clinical course, however, is variable, with some patients living less than a year while others survive for more than 10 years. Therefore, many attempts have been made to define risk groups in MCL. In particular, a higher proliferation index of the tumor cells has been associated with shorter survival. Recently, the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) demonstrated that the clinical course in MCL could be accurately predicted by gene expression profiling of tumor specimens. More than 50% of the genes associated with inferior outcome were derived from the “proliferation signature” that is more highly expressed in dividing cells. A gene expression–based outcome model was constructed, in which the proliferation signature average represents a linear variable that assigns a discrete probability of survival to an individual patient.

In this study, we asked whether the continuous increase of clinical risk in MCL patients, as shown by increasing expression of the proliferation signature, could also be mirrored by analysis of the Ki67 index, a widely accepted marker of cell proliferation in daily pathologic practice. Proliferation indices were assessed in 134 patients with MCL by staining representative slides with the monoclonal MIB1 antibody (DAKO, Copenhagen, Denmark) directed against the Ki67 antigen. The numbers of positive cells were recorded by 2 observers in increments of 10% and the resulting scores were averaged. No significant interobserver differences were noted (accuracy, 0.01; precision, 0.06). Median age of the patients was 65 years, and 121 patients received monoagent or multiagent chemotherapy. Clinical follow-up ranged from 1 month to 246 months, with a median of 24 months.

To continuously monitor the influence of increased proliferation on survival, patients were divided into proliferation groups, with Ki67 indices of 20% or less (n = 62), 21% to 40% (n = 32), 41% to 60% (n = 25), and more than 60% (n = 15). Kaplan-Meier analysis resulted in dramatically different survival curves, with median survival times of 53 months, 33 months, 19 months, and 13 months, respectively (P < .001, log-rank and Wilcoxon tests; Figure 1).

These curves are very reminiscent of those obtained after assigning patients to quartiles according to their gene expression–based proliferation signature averages. Five-year survival rates in the respective groups were 47% (confidence interval [CI]: 29%-64%), 32% (CI: 11%-53%), 31% (CI: 10%-53%) and 25% (CI: 3%-48%). No particular clinical characteristics were associated with defined proliferation groups. Moreover, in a multivariate analysis of risk factors in a Cox regression model, the Ki67 index emerged as the only independent variable predicting survival (P < .001).

In MCL, both primary and secondary genetic alterations target the integrity of the cell-cycle machinery and/or DNA damage pathways. Therefore, the quantitative measurement of proliferation can be viewed as an integrator of various oncogenic events in MCL. Given the pivotal impact of tumor cell proliferation on survival, stratification of MCL patients according to this parameter can be expected to have a profound effect on therapeutic options in risk-adapted strategies. Here we demonstrate a tight correlation between the Ki67 index of tumor cells and survival in MCL in a semilinear fashion and suggest that this marker may be useful in the stratification of patients in future clinical trials.

References

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