A number of investigators have provided data supporting the value of CD49d expression on B leukemia cells in chronic lymphocytic leukemia (CLL) as an independent prognostic variable. These studies used a variety of clinical end points including overall survival (OS), time to treatment (TTT) or treatment free survival (TFS). The factors included in multivariate analyses of these studies also differed. Unresolved issues regarding the prognostic value of CD49d assessment in CLL included the choice of the optimal cut-off to define positivity and CD49d prognostic value in patients subsets defined by other standard prognostic factors.

Studies published by 30 April 2011, reporting an association of high CD49d expression on B CLL cells, measured by flow cytometry, and end-points were identified by Medline search. Additionally, we performed a manual review of abstracts presented at the congress of the American Society of Hematology from 2006 to 2010. CD49d was used as a categorical variable, as coded in original studies. We identified 6 published studies and one abstract for inclusion. All authors agreed to provide individual data on the patients in these publications as well as unpublished data on additional patients to be used for replication analysis. Four authors also submitted updated follow-up data.

We collected the following variables: date of diagnosis, OS, TTT/TFS, CD49d, CD38, ZAP-70, immunoglobulin mutational (IGHV) status, del17p and del11q chromosomal aberrations, age, stage, ALC, and β2 microglobulin concentration. Data from 3146 individual patients was available with 261 subsequently excluded due to missing end point and/or CD49d data. Of 2771 patients with valid data, 1405 (51%) were included in the previous publications and 1366 (49%) were unpublished. Before starting analyses a decision was made to perform meta-analysis on published data and use data from previously unpublished data as a validation cohort.

Pooled CD49d hazard ratio for OS was 2.62 (1.94-3.55) (Fig.1). In bivariate analysis, the prognostic value of CD49d was confirmed and of comparable value in patients subsets defined by CD38 and ZAP-70 expression, IGHV status, unfavorable chromosomal aberrations (Fig. 2). Finally, we performed a multivariate analysis including CD49d, CD38, ZAP-70, IGHV status, del17p and del11q. CD49d was significantly associated with shorter overall survival in this adjusted model, with a hazard ratio of 2.47(1.17-5.21). Inspection of histogram and martingale residuals plots of CD49d in each study and in pooled data (Fig. 1, 2) failed to show a recognizable cut-point. Accordingly, rather than using a data driven approach, these analyses suggest choosing a cut-point on pure distributional criteria or by a data independent approach. Analysis using such a strategy is underway with plans for validation in the cohort of 1366 unpublished patients.

References

Shanafelt TD, O'Brien MT, Macko RF et al. Blood 2011; 117:1492-1498

CONCLUSIONS

Preliminary results of a meta-analysis using individual patient data from >1400 patients confirm the association of high CD49d expression with short OS independent of other prognostic parameters. These findings may have implication for patient’s stratification in future prospective studies and potential therapeutic efforts to target CD49d or CD49d signaling.