Peripheral blood blast clearance during induction therapy in acute myeloid leukemia

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polymerase chain reaction (RT-PCR) cyclin D2 mRNA was overexpressed. Conventional cytogenetic analysis yielded 4 mitoses with a normal karyotype. Interphase FISH performed with LSI IGH/CCND1 Dual Color, Dual Fusion Translocation Probes (Vysis, Downer’s Grove, IL) was negative for the t(11;14)(q13;q32), but demonstrated rearrangement of the IGH locus. Q-banded karyotype established from a bone marrow sample was 43,XY,−1,der(8)t(8;8)(p23;q13),−11,−13,add(15)(p11),der(17)t(1;17)(p22;p12),add(21)(q22),−22, +mar[p2]/46,XY[17]. FISH performed on bone marrow cells with the LSI IGH Dual Color, Break Apart Rearrangement Probe (Vysis), showed a rearrangement of the 14q32 region (Figure 1G). Because of apparent cyclin D2 overexpression, the tumor cells were investigated for a CCND2 rearrangement, using a break apart FISH assay as previously described.4 A break in the CCND2 locus was clearly demonstrated, with the telomeric probe mapping to 14q32 (Figure 1H). The short arms of both chromosomes 12 were normal, demonstrating a derivative 14 through a cryptic t(12;14)(p13;q32) translocation. Interphase FISH confirmed a CCND2 rearrangement in the lymph node (Figure 1I).

This is the first description of a cyclin D1-negative MCL with a t(12;14)(p13;q32) and cyclin D2 overexpression. Of the 4 cyclin D1-negative/cyclin D2-positive MCL previously reported, 2 were found to harbor a genetic alteration of the CCND2 gene, due to a translocation to the IGK locus.4,5 Our findings in the current case confirm that CCND2 is recurrently targeted by chromosomal rearrangements in cyclin D1-negative MCL, and identify IGK as a previously undescribed translocation partner. By analogy to other translocations involved in B-cell lymphomas, one would have expected to find this translocation more often. Interestingly, the t(12;14)(p13;q32) translocation has, to date, not been described. This is likely due to the rarity of true cyclin D1-negative MCL with CCND2 alterations but also to the cryptic nature of this rearrangement.

Systematic FISH investigation of suspected cyclin D1-negative MCL overexpressing cyclin D2 without obvious 12p13 and/or 14q32 rearrangements might lead to the identification of additional cases harboring this hitherto unrecognized translocation.

To the editor:

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Elliott and colleagues have reported in a group of 73 patients with acute myeloid leukemia (AML) that the time to clearance of peripheral blood blasts (PBB) during standard induction therapy is a strong predictor of both overall (OS) and relapse-free survival (RFS).1 We have previously shown2 in 30 AML patients that the kinetics of PBB clearance is a predictor of complete remission (CR). Thus, the 2 studies have in common the objective to obtain the maximum predictive information from the analysis of peripheral blood (ie, a much less invasive procedure than bone marrow aspiration); however, their results differ in several respects.

(1) The study reported by Elliott et al was retrospective whereas ours was prospective. (2) Elliott et al assumed that PBB clearance is a surrogate of in vivo chemosensitivity, but their study was carried out only on responder patients whose leukemic cells are, by definition, at least sufficiently chemosensitive for the patients to achieve CR; our study, instead, was carried out on unselected consecutive patients. (3) In the study by Elliott et al, PBB clearance was evaluated by differential count; in our study we identified by flow cytometry for each patient at the time of diagnosis a population of leukemic cells with aberrant immunophenotype (LAIP), and then determined absolute LAIP-positive blast counts on each of the first 5 days of treatment. Approval was obtained from Careggi Hospital institutional review board for this study. Informed consent was obtained in accordance with the Declaration of Helsinki.

By our approach (having doubled our series2 to 61 patients), we have observed from day 2 (ie, within 24 hours from starting therapy) a clear dichotomy between responders and nonresponders (Figure 1A): indeed, the difference between the responders (Figure 1A): indeed, the difference between the medians in the 2 groups is statistically significant from day 2. CR took place in 31 of 41 (76%) patients who had a reduction greater than 2 logs on day 5; but in only 1 of 20 (5%) patients who had a lesser reduction.

Unlike Elliott et al, in our series we do not yet have long-term follow-up data. However, because we found that peripheral blood LAIP-positive cell clearance correlates with bone marrow LAIP-positive residual disease (LD14; see Figure 1B), and residual disease in turn is known to correlate with RFS,3,5 it is reasonable to assume that PBB clearance will correlate with RFS. Thus, the combined data provided by Elliott et al and by our study demonstrate that from peripheral blood analysis it is possible to obtain strong predictors of both CR and RFS: in this respect the 2 studies are complementary. We concur

References

therefore in the hope that PBB clearance could be of help also with respect to tailoring treatment.

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We thank Professor Lucio Luzzatto for his support and precious collaboration in manuscript reviewing.

Contribution: G.G. and F.M. designed research, performed cytofluorimetric analysis, analyzed the data, and wrote the paper; S.B. performed cytofluorimetric analysis and performed statistical analysis; F.L. and A.B. evaluated patients and reviewed the paper; and S.B. performed cytofluorimetric analysis.

G.G. and F.M. contributed equally to this study.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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