CORRESPONDENCE

Primary Plasma Cell Leukemia and Multiple Myeloma: One or Two Diseases According to the Methodology

To the Editor:

Recently, García-Sanz et al. reported a series of 26 patients with plasma cell leukemia (PCL) in whom a number of biological parameters were studied, with particular emphasis about measure of DNA cell content by flow cytometry and detection of numeric chromosomal aberrations by interphase fluorescent in situ hybridization (FISH). For the purposes of comparison, the same parameters were tested in a series of 56 multiple myeloma (MM) patients. Their data, as presented, showed clear differences between the PCL and MM patients studied.

Firstly, all except 1 PCL patient studied showed a normal DNA content, whereas most MM patients (57%) showed a hyperdiploid DNA content.

Secondly, FISH studies using 15 chromosome-specific probes performed in 13 PCL and 56 MM cases showed statistically significant differences between PCL and MM for the following chromosomes: −13 (84% in PCL and 26% in MM), +9 (9% in PCL and 52% in MM), and +6 (6% in PCL and 32% in MM). Although chromosome 3, 7, 11, and 15 were found trisomic in MM cases only, the results of the statistical analysis regarding these defects are not mentioned. On the other hand, no difference was found for chromosome 1 involvement (43% in PCL and 37% in MM). The used chromosome 1 probe hybridized to the 1q12 heterochromatic region, making trisomy of chromosome 1 indistinguishable from the presence of a 1q chromosome derivative, a frequent finding in these pathologies.

The investigators concluded that, in PCL and MM, the DNA cell content and cytogenetic characteristics are different, leading to a different disease evolution.

We do not agree with these results, because we think that the techniques used, ie, flow cytometry and FISH with centromeric probes, are not appropriate to compare genetic aberrations in PCL and MM patients because they missed a number of aberrations detected by other techniques.

Whereas flow cytometry is a good technique to detect hyperdiploidy, it is not able to detect a minor error in DNA content such as a small hypodiploid clone or, moreover, pseudodiploid aberrations. Zandecki et al. used a different technique to appreciate the plasma cell DNA content (histochemical staining with computed analysis), found that 58.7% of patients were hyperdiploid, as reported by García-Sanz et al., but they also detected 24% patients with hypodiploidy and 4.3% with biclomality among a series of 46 MM patients. Elsewhere, conventional cytogenetics (CC) in stage III MM and in PCL cases lead to informative analysis in more than 70% of cases studied. Using CC, we studied a series of 81 MM patients with an abnormal karyotype and found 2 different cytogenetic patterns based on chromosome number: a hyperdiploid pattern (54%) with recurrent trisomies 3, 5, 7, 9, 11, 15, and 19 and a second pattern (46%) showing either pseudodiploid, hypodiploid, or near-tetraploid karyotypes. In this study, a prognostic correlation was found between the cytogenetic pattern and overall survival: hyperdiploid patients had a longer survival than patients belonging to the pseudo/hypo-near-tetraploid group.

In the same way, a recent conventional cytogenetic study of 13 primary PCL patients showed that 12 of 13 had an abnormal clone. A hypodiploid karyotype was found in 9 cases and a pseudodiploid was found in 2 cases. It was concluded that PCL patients share a poor prognosis with MM patients with a hypodiploid karyotype.

From a cytogeneticist point of view, we do not find any difference between plasma cell leukemia and hypo/pseudo/near-tetraploid multiple myeloma associated with poor prognosis. We think that PCL and MM are, in fact, the same disease. PCL could be is a fulminant form of MM and could be compared with those rare cases of chronic myeloid leukemia showing an acute phase at presentation.

Nicole Véronique Smadja
Laboratoire de Recherche en Cytogénétique Hématologique
Hôpital Saint Antoine
Paris, France
Christian Bastard
Laboratoire de Génétique Oncologique
Centre Henri Becquerel
Rouen, France
Christophe Brigaudeau
Laboratoire d’Hématologie
Hôpital de Limoges
Limoges, France

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Response

We are pleased for the interest that Smadja et al have demonstrated on our report, in which we report on the clinical and biological characteristics of a series of primary PCL. In their letter, they add cytogenetic information on 81 multiple myelomas and give a reference submitted for publication concerning 13 primary PCL, concluding that MM with pseudoploid, hypoploid, or near tetraploid karyotypes show similar genetic characteristics as compared with PCL. According to this information, they conclude that both diseases are the same, which would be in contrast to the conclusion that presumably we support in our report. Actually, in our previous publication, we just concluded that, because PCL and MM show overall distinct clinical, immunophenotypic, DNA ploidy, and cytogenetic characteristics, the link between both diseases remains unclear. In this sense, the apparent discrepancies between these investigators and us would be merely based on data interpretation.

Actually, a careful analysis of the information reported by Smadja et al would support our own data, even considering that different technical approaches were used for the analysis of chromosomal aberrations. They report on 81 MM, in which 54% are hyperdiploid (this prevalence is almost exactly the same as the 56% of MM with a DNA index >1 identified in our series). In contrast, no hyperdiploid PCL were found by Brigadeau et al among 13 cases tested, which is also coincidental with our experience (series 0/22 PCL had a DNA index >1). It is obvious that these differences favor the notion that, overall, PCL and MM are different diseases.

The most relevant cytogenetic molecular marker of PCL is the deletion of the Rb gene, located at chromosome 13, because it was present in the great majority of our PCL cases (86%). Nevertheless, this is not a specific marker of PCL, because a subset of myeloma patients also share this chromosomal change. This subset of patients display an unfavorable prognosis. Therefore, it could be argued that these MM patients are tightly related to PCL. However, upon analyzing other chromosomal changes, we observed that a high proportion of MM cases with monosomy 13 concomitantly show trisomy 9 (67% of cases) and trisomy 6 (33%), whereas none of these changes was observed in our PCL patients. Moreover, as shown in Fig 1, the survival of MM patients with monosomy 13 was significantly better than in those PCL patients with the same chromosome abnormality (median survival, 16 and 7 months, respectively; *P* = .011). Based on these results, it could be speculated that the occurrence of a deletion in the closer area of the Rb gene would be a critical alteration that changes the clinical behavior of the disease. However, this alteration would appear in MM in a different moment of the clonal evolution as compared with de novo PCL. In addition, from the biological point of view, we described in our report several other parameters, including the proliferative activity, extramedullary involvement, LDH serum level, immunophenotype, response to therapy, etc, that were also different between MM and PCL, suggesting that MM and PCL are different.

Despite these data, we think that the answer to the question on whether PCL and MM are the same disease remains open. In this sense, we still can recognize overlapping cases that accomplish MM or PCL criteria but display clinical or biological characteristics of the other form. This was already reported in our publication. This fact could lead to the hypothesis that MM and PCL belong to the same group of diseases (here we should use the unspecific term monoclonal gammopathies), but there is a different pattern in the accumulation of genetic alterations leading to a different clinical behavior in the 2 forms of the disease. Because the clonal evolution and the genetic way to acquire aberrations depend on many circumstances, this could explain why there exist some overlapping cases.

R. García-Sanz
A. Orfão
J.F. San Miguel
Department of Hematology
University Hospital of Salamanca
Salamanca, Spain

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Polymerase Chain Reaction Analyses Should Be Used as a Basis for Clinical Decision Making in Patients With Chronic Myelogenous Leukemia

To the Editor:

The report of Faderl et al1 deals with the question of whether polymerase chain reaction (PCR) analysis, used to detect minimal residual disease in patients with chronic myelogenous leukemia (CML), should be used in clinical decisions. The authors’ view on the ability of PCR to predict relapse of the disease is very critical. However, all of their considerations, and consequent conclusion, are based only on qualitative PCR and some static results of quantitative (Q)-PCR. They do not take into account the sequential analyses of residual disease by Q-PCR and they quite ignore the advantages of Q-PCR for follow-up of the dynamics of CML, which have been confirmed by many investigators.2-5 It was already shown several years ago that qualitative PCR confirming the presence of the BCR-ABL transcripts in patients after bone marrow transplantation (BMT) can only identify patients belonging to a group with elevated risk of relapse, but it is only of a limited predictive value for the disease evolution in individuals of this group. Only the Q-PCR, by determining the amount of BCR-ABL transcripts at regular time intervals, can find an increasing level of BCR-ABL transcripts indicating activity of the malignant clone and thus predict the impending clinical relapse.2,5

This is also our experience. At our institute, the Q-PCR was introduced in 1994; since then, it has been used for routine monitoring of the BCR-ABL level in patients with CML after BMT. The results of the monitoring have been used as a basis for making clinical decisions. The assay permits absolute quantification with a sensitivity of 10−3 and was proved to be precise and reliable by comparing its results with the mathematical model of competitive PCR.8 Before BMT, each patient is tested by multiplex qualitative reverse transcriptase-PCR (RT-PCR),10 which is capable of identifying any of the BCR-ABL transcripts to exclude some atypical rearrangement and to prevent false-negative results in post-BMT monitoring; this is the answer to the anxiety of Faderl et al1 about false-negative results in diagnosis and monitoring of residual disease in CML. Patients after BMT are followed-up by qualitative PCR at regular time intervals suggested by the group of European Investigators on CML (EICML group),3 ie, at 2- to 3-month intervals in the first year after BMT, when 2-step PCR results are negative, and at 6-month intervals during further years of PCR negativity. In patients with persistent post-BMT or reappearance of PCR positivity, quantitative PCR analyses are performed at 1-month or shorter intervals. In our own experience, this time schedule is necessary to enable an early detection of imminent disease relapse. Molecular (PCR) relapse is defined dynamically as a 10-fold increase of PCR positivity5 without any signs of cytogenetic relapse. Therapeutic intervention, to be most efficient, should start at the molecular relapse. If regular sequential analyses by qualitative and quantitative PCR are performed, comparison of the 2 methods can be performed. The group of patients with permanent BCR-ABL positivity found by qualitative PCR assay can be further divided into 3 groups by Q-PCR: groups with increasing, stable, or decreasing level of BCR-ABL transcripts. These quantitative results clearly show different evolution of the disease in individual positive patients; therefore, different clinical decisions should be made on the basis of these results.

From our experience, we do not suppose that a definite level of BCR-ABL transcripts, a threshold as the investigations mention, can be found “above which a patient is likely to relapse or, conversely, below which remission is sustained.” A patient with a level of BCR-ABL transcripts below such a definite threshold cannot be said to be in remission if the amount of the BCR-ABL transcripts is permanently increasing. On the other hand, a patient with a relatively high but stable level of BCR-ABL positivity can be in a stable state without relapse for several years, although the danger of relapse is very high in this case. However, we assume that a definite level of BCR-ABL transcripts should be given as the threshold that marks the last appeal to start therapy before cytogenetic or even hematological relapse is diagnosed. We cannot agree with the investigators’ apprehension of injuring the patients due to decisions made on PCR assay “given the significant morbidity and mortality associated with aggressive therapeutic interventions aimed at molecular disease eradication.” The aim of Q-PCR is quite the opposite—not to force clinicians to eradicate leukemic clone under detectable level of PCR at any cost, but to show the increasing proliferative activity of the malignant clone still in the time of full clinical and cytogenetic remission when malignant clone is not too numerous and when nonaggressive therapy (low doses of DLI) is shown to be very efficient. The intention of Q-PCR monitoring is to prevent clinical relapse when treatment efficacy is low despite very aggressive therapeutic intervention.

The findings of BCR-ABL transcripts in leukocytes from healthy adults cannot decrease the validity and importance of Q-PCR tests for predicting disease relapses after BMT. In the study of Bose et al,11 the overall sensitivity of Q-PCR assay used in healthy individuals is approximately 40 times higher than that used in practice; the finding of this normal positivity is, thus, highly improbable. Moreover, such a positivity would appear as a low incidental positivity, having no predictive value for the disease relapse. On the other hand, long-term highly sensitive sequential Q-PCR analyses showing a permanently increasing amount of BCR-ABL transcripts in healthy individuals should separate those predisposed to the outbreak of the disease. However, this cannot be used in practice.

As to technical pitfalls of the PCR, such as sample contaminations, etc, we do not believe that they can influence the results of the minimal residual disease monitoring at present. We hope that every responsible


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Nicole Véronique Smadja, Christian Bastard and Christophe Brigaudeau

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