within a defined environment or niche, as do leukemic cells. A multiscale analysis of Bcr-Abl in affecting hematopoietic cells at different stages of development and their interactions with the microenvironment and immune cells should yield a more accurate picture.

Perhaps the Maltese Falcon will never be found. Let us hope a different fate awaits the CML-initiating cell. Despite several caveats, this report does bring us much closer to finding, understanding, and eradicating the CML-initiating cell.

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CLINICAL TRIALS

Comment on Pott et al, page 3215

The adulthood of MRD detection in MCL

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In this issue of Blood, Pott and colleagues correlate clinical outcome and MRD results in MCL. The analysis by real-time quantitative PCR of 259 patients included in 2 international randomized trials indicated MRD as an independent outcome predictor. The good large-scale applicability and high predictive value indicate that MRD detection is ready to be assessed as a decision-making tool in MCL.

The prognostic value of minimal residual disease (MRD) detection by polymerase chain reaction (PCR)-based methods in mature lymphoid tumors has been debated over nearly 2 decades. Following the seminal works of Gribben et al in autografted follicular lymphoma (FL) patients, the prognostic role of MRD has been demonstrated in many different mature lymphoid neoplasms and is now well established in multiple myeloma, FL, and mantle cell lymphoma (MCL). From a clinical perspective, the contribution of MRD studies has been particularly prominent in MCL. In the pre-rituximab age, the specific chemoresponse of MCL patients was outlined by their extremely low rate of molecular remission as opposed to FL patients. The subsequent improvement of treatment paradigms in MCL was heralded by MRD studies. Magni et al showed that the introduction of high-dose Ara-C and rituximab produced an unprecedented level of cytoreduction. Later, Pott et al demonstrated the predictive value of MRD monitoring in a retrospective analysis of 29 patients. Finally, Andersen et al showed the feasibility of preemptive treatment of molecular relapse in reducing the risk of overt clinical recurrences. Over this long period of time, methodological approaches have also evolved as qualitative PCR has been implemented and often substituted by real-time quantitative PCR.

The prognostic role of MRD is thus fairly established in mature lymphoid tumors. Nevertheless, concerns on its use for decision making are still widespread among clinicians due to the following issues: (1) patient series are small, often retrospective, and arising from single-center experiences; (2) MRD results can be treatment-biased (ie, some treatments might have superior molecular performances in the absence of a real clinical benefit); (3) the value of MRD is well documented in the autologous stem cell transplantation (ASCT) field but needs to be proved in the context of conventional therapy; (4) MRD assesses disease kinetics exclusively in peripheral blood (PB) and bone marrow (BM), but is unable to monitor disease evolution in nodal sites; (5) even if potentially useful, careful molecular monitoring is too cumbersome to be performed in the context of large, prospective phase 3 trials; and (6) MRD detection is not a standardized tool and comparability among different institutions has not been proven.

The work of Pott et al addresses several of the previously mentioned points. MRD was included here as a secondary endpoint in the context of 2 large international phase 3 trials (NCT00209222 and NCT00209209 [www.clinicaltrials.gov]) on a panel of 259 patients, representing a major sample size escalation compared with previous studies. The population included young and elderly patients. Treatment modalities included both conventional and ASCT-containing programs. The 90% success rate in obtaining a PCR-amplifiable tumor-specific marker in such multicenter (and multinational) context confirms the broad applicability of MRD in MCL. MRD proved predictive in all disease contexts and appeared to be unbiased even in the setting of maintenance treatment. The good prognostic discrimination observed in the elderly trial is a clear indication that the value of MRD monitoring is not restricted to specific ASCT-based treatment schedules. The article also focuses on the value of different tissue sources with respect to MRD analysis. Whereas MRD levels were comparable in BM and PB at diagnosis, disease clearance appeared more effective in PB. This indicates that MRD detection in the BM is a very effective sensor of global disease activity and not a mere indicator of local persistence of residual tumor burden. Nevertheless, the growing number of patients who have been assessed for MRD in this and other studies will allow verifying whether the few relapses arising among PCR-negative patients display specific clinical peculiarities compared with those heralded by PCR-positive results.

There are some limitations to this study. The overall population enrolled in the 2 trials of the European MCL Network is wider compared with the population analyzed in the report, as a large proportion of patients are still under evaluation. The 2 randomized trials are still blinded, preventing a detailed evaluation.
of the impact of different treatment arms on MRD kinetics. The observation time is still fairly short. I expect that these issues will be the object of future updates of the study. Nevertheless, the importance of results so far achieved by MRD analysis is clear, as documented by the inclusion of MRD as secondary endpoint in most new-generation MCL trials, such as the recently launched III–MCL–0208 trial from Intergroupe Italiano Linfomi/European MCL Network (Clinic Gov EudraCT Number 2009-012807-25). In the near future, prospective studies in MCL will probably also address the use of MRD as a surrogate marker, suitable for risk-adapted treatment.

As MRD becomes increasingly important in the clinical management of MCL patients, the issue of standardization and adoption of consensus definitions is becoming critical. During the Second International Symposium on MRD assessment held in Kiel, Germany, in September 2008 (proceedings are currently in the publication process), expert consensus has been established on a number of technical requirements and definitions suitable for clinical use. Moreover, several MRD laboratories have started to perform quality-control rounds in the context of the European Study Group for MRD detection in acute lymphoblastic leukemia and non–Hodgkin lymphoma (now called Euro–MRD). The ultimate aim of such an effort will be the full standardization of PCR techniques in mature lymphoid disorders as already achieved in the acute lymphoblastic leukemia field.

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