

ADVANCES IN LLM

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Benefits of Minimal Residual Disease Negativity in the Therapy of Chronic Lymphocytic Leukemia

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H&O What is minimal residual disease (MRD) in chronic lymphocytic leukemia (CLL)? What are the available technologies to identify MRD? How does sensitivity of these methods compare in assessing MRD?

NK MRD in CLL is usually assessed at the end of a treatment protocol. Typically this is not done until several weeks or a few months after the cessation of therapy. This is done for several reasons, including most prominently, the fact that marrow suppression secondary to treatment may persist, and because some treatment protocols have been observed to have continuing impact on disease level even after the cessation of active treatment.

Using the NCI-WG 1996 criteria where no imaging studies or X-rays were advocated, the usual studies done to detect MRD in the patient who had a complete response (CR) or a nodular partial response (nPR) were either multi-color flow cytometry or molecular techniques such as polymerase chain reactions (PCR). The former uses 3 or 4 color flow that detects cells with a "CLL immunophenotype", and the latter assays target fusion regions of chromosome aberrations and clone (allele)-specific immunoglobulin. These techniques may have exquisite sensitivities of around 1×10^4 to 1×10^5 cells per μL . With this as the setting for conducting MRD assays, the ultimate goal is to reach a "negative" MRD state, which is no detectable CLL B-cells using either assay type. However, in most previous studies, residual MRD is still evident with these techniques, even in a patient with CR,

implying that there are still circulating leukemic CLL B-cells. Since almost all CR patients relapse, clearly the achievement of a NCI-WG 1996 criteria CR is compatible with significant amounts of residual malignant cells.

Despite the discouraging fact that most patients have detectable MRD post-therapy, the more effective therapies available now have mandated the use of these sensitive MRD assays in order to gauge just how effective and "deep" the therapies have reduced the leukemic CLL B-cell burden in a given patient. Since multi-color flow cytometry is now relatively simple, available results within a day are routine in most laboratories, and it is emerging as the method of choice for MRD assessment.

Standardization and adoption of a validated flow method is essential to the consistent interpretation of MRD results in the context of clinical trials. To that end, the European Research Initiative on CLL (ERIC) has worked on developing a consensus for MRD assessment. This work has found that a level of a single CLL cell in 10,000 white cells per μL can be reliably detected by either MRD flow cytometry or allele-specific PCR; they define MRD negativity in CLL as less than a single CLL cell in 10,000 cells per μL , and that thus can be done in blood of CLL patients. The only exception for this is when monoclonal antibodies used for eradication of disease are included in treatment protocols, as marrow lags behind blood clearance of leukemic B cells. The standardization of these methods in laboratories linked to randomized clinical trials, and testing the relationship of MRD levels to progression-free survival (PFS) and overall survival (OS), is essential if we are to make sense of this type of work on MRD.

Importantly, allele-specific PCR is approximately a log more sensitive than MRD estimation by flow; however, because it is more expensive and still relatively tedious to

Table 1. Response Evaluation in Chronic Lymphocytic Leukemia MRD Assessment

	MRD Flow	RQ ASO-PCR
Applicable patients	>95%	85%–95%
Sensitivity limit	0.01%	0.001%
Quantitative range	0.1–0.01%	0.01%
Cost and complexity	Moderate	Initially high, follow-up low
Pre-treatment material required	Preferable	Essential
Processing time	Hours	Weeks

MRD=minimal residual disease; RQ ASO-PCR=real-time quantitative allele-specific oligonucleotide polymerase chain reaction.

set up, its use is not standard in routine practice (Table 1). In clinical trials that are research protocols and where a true MRD eradication is a desired end point, then allele-specific PCR is likely to have a more prominent role. Figure 1 outlines the levels of sensitivity of the various methods for assessing MRD in CLL.

H&O Are there any clinical trials that assessed MRD and its benefit in CLL patients? What are the known or postulated clinical benefits of MRD negativity in the treatment of CLL? What are the toxicities of such approaches?

NK In patients with CLL, the prognostic significance of MRD is still a matter of debate, as the majority of patients remain MRD positive after conventional treatment. In addition, the evaluation of MRD has lagged behind in this disease compared to other hematologic malignancies such as chronic myelogenous leukemia or acute promyelocytic leukemia, where the benefits and prognostic utilization of MRD status are clear. However, a true elimination of MRD has been linked to improved survival and has become an important clinical goal in many diseases, and this is likely to be the case in CLL. While overall response rates with current chemotherapy treatments are superior to those seen with single agents (eg, fludarabine, chlorambucil), many CLL patients still fall short of achieving a CR and certainly of having a negative MRD status.

However, the ability to achieve a negative MRD status in upfront first line treatment for CLL patients is now within reach in a significant percent of patients. The highly active chemoimmunotherapy regimens can generate no detectable MRD as measured by highly sensitive flow cytometry or PCR-based assays. Interestingly, these

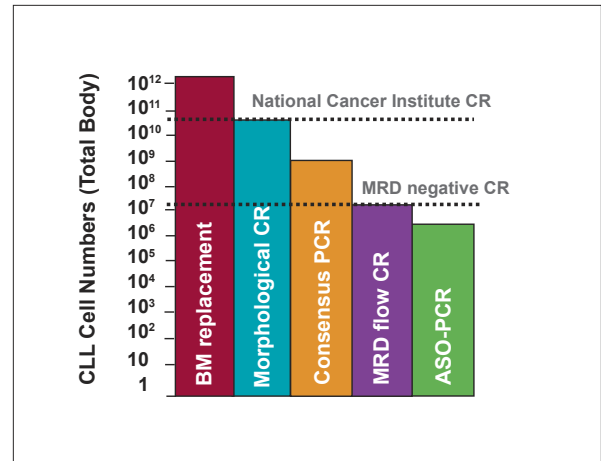


Figure 1. Neoplastic cells present in CLL (various assessment techniques): National Cancer Institute CR vs MRD-negative CR.

ASO=allele-specific oligonucleotide; CLL=chronic lymphocytic leukemia; CR=complete response; MRD=minimal residual disease; PCR=polymerase chain reaction.

Adapted from data by Peter Hillmen, MD, PhD.

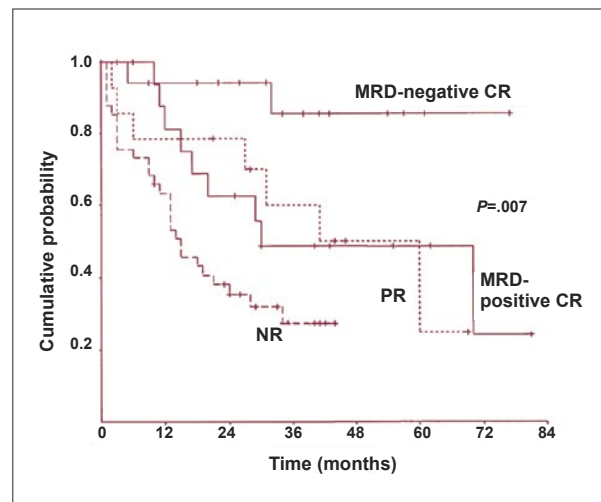


Figure 2. Median survivals for MRD-positive patients with CR, patients with PR, NR; median survivals for minimal MRD-negative responders has not been reached.

CR=complete response; MRD=minimal residual disease; NR=non-responders; PR=partial response.

Adapted from Moreton, et al. *J Clin Oncol.* 2005; 23:2971-2979.

studies have found low to no MRD in CR patients but some are even seen in partial response (PR) patients. In the latter case, this may be the result of a PR due to prolonged drug-induced cytopenias but not other residual diseases. It also indicates that the recent suggestion to incorporate computed tomography scans of chest, abdomen, and pelvis, in assessing residual disease may be relevant if CLL patients are in a CR or PR.

Nevertheless, some studies have found that MRD negative patients have a longer PFS and OS than those who still have measurable residual disease (Figure 2). The ability to achieve a truly negative MRD should be associated with very prolonged OS, or even cure, but that is still not proven. Since we can now accurately measure MRD following the completion of upfront therapy, we are in a position to define cohorts of patients who should probably receive more therapy. This is complicated by 2 aspects: First, we still have to prove that some detectable MRD in certain patients is compatible with prolonged survival versus patients with no detectable MRD. Second, there may be certain “high risk” patients as defined by novel risk factors (Kay NE, et al. *Leukemia*. 2007;21:1885-1891) that are far more likely to quickly relapse with residual MRD than low risk patients. At any rate, the potential correlation between negative MRD status and significantly prolonged PFS will require further assessment in randomized clinical trials.

The agent currently tested the most frequently as “consolidation therapy” for patients with residual disease at the completion of induction therapy is alemtuzumab (Campath, Bayer Healthcare). These trials have found some encouraging features including the fact that some CLL patients with MRD can approach true negative MRD, and that this status is associated with enhancement of PFS. Unfortunately, this approach has been found to result in severe infectious complications including fatal outcomes for a significant number of patients. Given these complications, it would seem prudent not to routinely incorporate this so called “consolidation therapy” for MRD positive patients outside of clinical

trials, and where modified doses and schedules of alemtuzumab or other agents, such as lenalidomide, that are not as prone to suppress the immune system of CLL patients are being used.

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