

Editorial

Implication of Minimal Residual Disease Assessment in Chronic Lymphocytic Leukemia Clinical Decision-Making

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Chronic lymphocytic leukemia (CLL) is the most prevalent adult leukemia in the western countries. It comprises approximately 7 percent of non-Hodgkin lymphomas [1]. In Canada, the median age at diagnosis is approximately 72 years [2]. There are approximately 4.6 new cases of CLL per 100,000 men and women per year based on 2009 -2013 cases [3]. In 2015, an estimated 14,620 people will be diagnosed with CLL in the United States and an estimated 4,650 will die from the disease. This represents 0.9% of all new cancer cases in the United State [1]. The five-year survival is approximately 80 percent in men and 85 percent in women [2].

New discoveries in genomics, classification, risk stratification and application of current and new therapies has shifted [4] the aim of CLL therapy from palliation to disease eradication, particularly for younger patients who account for almost a third of the entire population with this disease. Moreover, using a plethora of prognostic markers enables prediction of the patients' outcome more accurately [5].

Four new CLL medications: ofatumumab, obinutuzumab and the kinase-directed therapies i.e idelalisib and ibrutinib were fully approved in the United States in 2014. All are now either approved or in the process of completing regulatory review in other countries [4]. The complete response (CR) rates from less than 10% with chlorambucil to 60% - 70% with some of the regimens currently under investigation [6].

CLL is a multicompartamental disease, nearly always involving bone marrow (BM), blood, lymph nodes, liver and spleen (macroscopically or microscopically) prior to treatment. Following treatment, 1 or more of these disease sites may act as a "reservoir" for residual disease [7]. MRD is an objective measure of disease status defined by the number of remaining leukemic cells in peripheral blood (PB) or BM following treatment. According to current international definitions, MRD negativity equals a quantitative detection of less than 1 CLL cell in 10,000 leukocytes (MRD level < 10⁻⁴). MRD assessment is currently recommended in clinical trials and is not recommended for routine clinical practice [8].

MRD assessment can stratify patients in CR into MRD-positive and -negative groups [9]. Low-level MRD does not equal complete disease eradication [10]. These residual cells except in the context of alloSCT are responsible for clinical relapse. The timing of relapse depends on the quantity of residual disease and kinetics of residual leukemia cell division [7].

Achieving MRD-negative remission at the end of treatment is one

of the most powerful predictors of PFS and OS, independent of the clinical response, the type or line of therapy and pretreatment prognostic features [11]. Current evidence suggests that in unselected patient cohorts an MRD level $\geq 10^{-4}$ is associated to a median PFS of about 2 years, whereas a MRD level < 10⁻⁴ predicts a median PFS of around 6 years [8].

The likelihood of achieving MRD-negative remission is lower for patients with high-risk prognostic features and those receiving less effective therapy. Additionally, in multivariable analysis, pretreatment high-risk characteristics, such as unmutated IGHV, ZAP70 positivity and del(11q) were associated with more rapid reappearance of MRD and shorter PFS [7]. TP53 mutated patients are less likely to reach MRD negativity [12].

MRD Assessment in CLL During First-Line and Advanced-Line Treatments:

- The assessment of MRD has become a very important endpoint of prognostic effect in the chemoimmunotherapy (CIT) setting. MRD positivity was associated with relapse and shorter survival [13].
- Median duration of PFS and overall response was longer for patients on advanced-line therapies achieving MRD-negative versus MRD-positive CR [14].
- Recent studies have demonstrated improved outcomes in CLL patients who achieve MRD negativity within 12 months of alloHSC [14]. The application of MRD monitoring to guide pre-emptive immune interventions or targeted therapies shows promise in preventing clinical relapse post allo HSC [15].
- MRD positivity in post-transplantation follow-up does not inevitably correlate with disease progression but may reflect evolving chimerism and graft-versus-leukemia activity over

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time [16]. Monitoring MRD at regular intervals gives a dynamic assessment of disease trends that is more meaningful than a single MRD assessment at 12 months post-transplant [15].

- Although autologous SCT is no longer considered a standard treatment in CLL, detection of MRD in peripheral blood or bone marrow within the first 6 months of transplant predicts a high risk of disease relapse [16].

Can MRD Status Guide Therapy in CLL?

One proposed goal of MRD assessment is to develop risk-adapted treatment strategies, which requires prospective testing in clinical trial [7].

- Patients with MRD at final response assessment could be candidates for treatment intensification, consolidation or maintenance strategies [10].
- Patients who achieve early MRD-negative status may be candidates for treatment de-escalation to limit treatment-related toxicity while maintaining the same efficacy [10]. The prediction of the individual remission duration gains importance in avoiding overtreatment in low-risk patients [10].
- FCR regimen can be associated with complications, particularly in elderly patients. There is concern about second malignancies, including myelodysplastic syndrome and acute myeloid leukemia in young patients with a longer life expectancy. Data suggest that early treatment cessation in patients who achieve MRD-negative status after 3 cycles of FCR may be feasible without compromising long-term disease control, but this requires prospective study [17].
- Achieving MRD negative status may reduce the likelihood of developing resistance mutations, although this remains to be proven [7].

Areas of Uncertainty

- Patients in MRD-negative PR had superior PFS than those in MRD-positive CR. Thus, achieving posttreatment MRD-negative remission with CIT may be more important than achieving clinical CR. For example, presence of residual lymph nodes of 1.5 cm by computed tomography may be explained by persistent viable tumor resistant to certain therapies, despite clearance of CLL from the blood and marrow or residual enlargement may represent fibrosis with no viable tumor [7].
- MRD assessment cannot generally be used to assess the efficacy of novel regimens such as ibrutinib as monotherapy or in combination with rituximab [7]. BCR signaling inhibitors are associated with long-term CLL persistence in blood and marrow despite effective disease control [13].
- BCR signaling inhibitors regimens are given continuously until disease progression [7] so, their clinical trials should focus on PFS and OS rather than the previously used conventional endpoints of PR, CR, and MRD status [14].
- There is no formal proof of a therapeutic benefit of re-treatment upon documentation of MRD positivity after an initial MRD-negative response compared to treatment at the time of clinical

relapse. Very few studies have demonstrated a clear benefit from MRD eradication or consolidation therapy in CLL [5].

Laboratory Assays

- MRD assessment is recommended in clinical trials using standardized protocols of either 4-color flow cytometry or IgV_H gene allele-specific oligonucleotide PCR [13]. They allow recognition of residual leukemic cells at a level of 10⁻⁴, which is now acknowledged as the standard level for MRD negativity [18].
- MRD assessment in PB is equally sensitive as that of BM [18]. If the primary purpose of the assay is to identify poor-risk patients who may benefit from consolidation and/or maintenance therapy, then blood assessment may suffice [10].
- BM aspirate is necessary to assess MRD in the first 3 months after completion of treatment with monoclonal antibodies-containing regimes [18]. Owing to the higher rates of MRD after treatment in BM, assessment of MRD in BM would achieve the highest negative predictive value for subsequent relapse risk [7].
- High-throughput sequencing (HTS) technology has already shown potential to detect MRD at the 10⁻⁶ level. Cells from blood, BM or cell-free DNA in plasma can be evaluated [7]. HTS-based testing of plasma may be evaluated in the future to detect MRD in lymph nodes, liver, and spleen which cannot be directly or easily detected in blood and BM [7].
- FLC methodology is being further refined; 6-color, 8-color, and 10-color methods were developed [19]. The latter allows combination of the required antibodies into a single tube assay and sensitivity approaches 10⁵ if 1.8x10⁶ total cells are analyzed [7].
- Addition of the tumor-specific antigen CD160 may achieve sensitivity of 0.01% to 0.001% in a 6-color, single-tube assay [9].

It may be tempting to use MRD assessment rather than clinical response in the future for guiding therapy at least in young, fit, progressive patients, aiming for reaching target of MRD level of 10⁻⁴ [11].

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