Journal of Oncology Research and Treatments

Mini Review Article Open Access

An Update on Minimal Residual Disease (MRD) Assessment in Mantle Cell Lymphoma (MCL): A Mini Review

Dayoung Jung*

Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Centre, 1515 Holcombe Blvd, Houston, TX, 77030, USA

Abstract

The field of minimal residual disease in most B-cell malignancies is critical. This is especially true for mantle cell lymphoma, a rare but aggressive subtype of non-Hodgkin's lymphoma. A recent review of available minimal residual disease assessment methods has shown promising results in mantle cell lymphoma, specifically in the advancement of circulating tumour DNA-based liquid biopsy methods. While there are various minimal residual disease markers in mantle cell lymphoma, finding the best suitable marker remains a problem yet to be solved. Because minimal residual disease monitoring is not yet validated in clinical trials, seeing studies that include such an assessment has become valuable in determining if it can accurately aid in identifying future prognostics and outcomes of a chosen therapy method. By using next generation sequencing methods, liquid biopsy is able to utilize various sample types, like circulating tumour cells, cell-free DNA, circulating tumour DNA, and etc., from a drop of blood to assess the molecular landscape of the tumour in a non-invasive manner. More recent updates on the basic methods, available markers, and liquid biopsy assessments in mantle cell lymphoma are described in this mini-review.

Keywords: Non-Hodgkin lymphoma; Minimal Residual Disease (MRD); Mantle cell lymphoma; Lymphocytic leukaemia

Introduction

Minimal Residual Disease (MRD) assessment in the field of hematological cancers is a topic of high interest as it has shown to predict relapses, be an independent prognostic factor, and be a good indicator of how a chosen treatment plan is doing. Sample preparation and assay choice play an important role in assessing MRD in most hematological diseases. While there are many assays available, Next-Generation Sequencing (NGS) is one of the most sensitive methods that is under active research. However, other methods, such as Polymerase Chain Reaction (PCR) and Multi-Parameter Flow Cytometry (MFC), are still commonly used. Sample preparation is especially important in MFC as its sensitivity depends on the number of white blood cells. A study compared a standard post-lysis sample preparation (Stain-Lyse-Wash or SLW) to a modified Euro Flow pre-lysis (Lyse-Stain-Wash orLSW) to assess the overall sensitivity in detecting MRD among multiple myeloma, chronic lymphocytic leukaemia, and B-non Hodgkin lymphoma patients. The latter LSW sample preparation achieved sensitivity at 10^{-5} with MFC for all patients, suggesting this modified method to be more widespread [1]. NGS methods arestill superior as it can generally reach a sensitivity of 10^{-6}. Liquid Biopsy (LB) is a term used to describe a non-invasive approach that utilizes a blood drop from a patient to evaluate the molecular landscape of various hematological malignancies *via* NGS methods. A study that used this method on Follicular Lymphoma (FL) for the first time demonstrated that despite the spatial genetic heterogeneity FL has, both lymph node biopsies and cell-free DNA (cfDNA) collected at diagnosis successfully identified all potential MRD markers [2]. While cfDNA can originate from tumour and non-tumour cells, circulating tumour DNA (ctDNA) primarily originates from tumour cells and comprises <1% of total cfDNA. While the exact mechanism of ctDNA release is still not known, it is a good marker to detect MRD in manyassays, including LB and NGS based methods. A prospective study that assessed MRD in Diffuse Large B Cell Lymphoma (DLBCL) patients using an NGS based assay found that while ctDNA can be isolated from these patients to detect MRD successfully, the practicality of implementing such a method in daily clinical use requires further studies due to cost and sample adequacy [3]. One of the most popular NGS methods to detect MRD is clonoSEQ, which combines both multiplex PCR and NGS techniques that can be applied to tumour-enriched samples. A study validating its analytical performance used both patient samples and cell lines of 3 different diseases, acute lymphoblastic leukaemia, multiple myeloma, and chronic lymphocytic leukaemia, and found that clonoSEQ based MRD detection results were robust with extremely low nucleotide sequence error rates [4].

Literature Review

Mantle Cell lymphoma (MCL) is a rare but aggressive type of B-cell non Hodgkin's lymphoma that invades both the peripheral blood and bone marrow in an invasive manner in about 90% of cases, making MRD detection quite favourable [5]. The field of MRD detection in MCL continues to evolve and recent studies can support this claim. A systematic review and meta-analysis of ten studies that looked into the association between MRD and survival outcomes in MCL patients found that MRD positivity post-induction and consolidation treatments were associated with poor Progression Free Survival (PFS) and Overall Survival (OS) [6]. In a preliminary report ofa multicentre phase II trial that evaluated both safety and efficacy of ibrutinib maintenance after chemo-immunotherapy in MCL patients, NGS-based MRD assessment showed that most patients were MRD negative. However, longer follow-up was needed to define a stronger correlation between MRD and PFS and OS to determine if ibrutinib maintenance has any clinical

***Corresponding author:** Dayoung Jung, Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Centre, 1515 Holcombe Blvd, Houston, TX, 77030, USA, E-mail: djung1@mdanderson.org

Received March 25, 2021; **Accepted** April 08, 2021; **Published** April 15, 2021

Citation: Jung D (2021) An Update on Minimal Residual Disease (MRD) Assessment in Mantle Cell Lymphoma (MCL): A Mini Review. J Oncol Res Treat S1: 002.

relevance [7]. While a different phase II trial saw successful MRD negativity in MCL patients who underwent obinutuzumab plus DHAP therapy, specific endpoints like PFS and OS weren't used to validate the association between MRD and survival [8].

A common standard of care for MCL is Autologous Stem Cell Transplantation (ASCT). To interrogate MRD in the autologous grafts, 17 paired MCL samples of FFPE and autologous stem cell grafts were used to identify MRD in the form of post-recombination immunoglobulin VDJ sequences. This was helpful in stratifying the patients per post-ASCT outcomes as higher MRD loads correlated with poorer PFS and OS, with a median 10 months vs. 27 months, and 25 months vs. 66.8 months, respectively, in comparison to those who had low or no MRD detected [9]. In patients who have undergone intensive chemotherapy followed by ASCT, an NGS based MRD detection method was able to identify early molecular relapse. In addition, cellular compartment (circulating leukocytes) provided higher sensitivity in comparison to the a cellular (cfDNA), which requires further investigation as this may have been due to availability of tumour target [10]. There are generally two commonly used MRD markers in MCL: the Immunoglobulin Heavy chain (IgH) rearrangements and the Bcl1-IgH rearrangement that derives from t (11;14) (q13;q32). In addition, studies have exploredthe possibility of finding other unique markers, such as SOX11 and CCND1. For example, a study looked to see if Immunoglobulin Kappa- deleting-element (IgK-Kde) rearrangements would be a suitable MRD detection marker in MCL. By using RQ/digital droplet-PCR methods, IgK screening was done and found in 76% of cases. This study suggests that a novel candidate target for MRD can be further investigated for validation in prospective MCL cases [11].

While the above highlights the on-going MRD studies in relation to MCL, it is important to note that the same applies for other hematological malignancies. Aforementioned, LB is a non-invasive method that uses a blood drop to assess the cancer genomic landscape at a given time. Before this, methods such as PET and CT scans primarilyrelied on tissue samples that were not only invasive but also suboptimal in sensitivity and required radiation exposure. In fact, studies have shown that LB can identify variants not identified in tissue analysis, providing it to be a more sensitive method [12]. While ctDNA analysis from these blood drops has become widely accepted, there are still limitations that need to be addressed. These include sensitivity limited by background noise, low recovery of cfDNA/ctDNA, and the dependence on mutation frequency. To improve from such barriers, novel methods are under active investigation to boost ctDNA performance in MRD detection. One way is differentiating between the fragments and patterns of healthy cfDNA vs. tumour-derived cfDNA. For instance, studies have shown tumour-derived cfDNA are generally shorter than healthy ones, suggesting fragment size could be a good way to distinguish DNA originating from the tumour [13]. Another way is to assess the epigenetic modification in cfDNA, which has shown that abnormal methylation patterns can be a poor prognostic marker for survival in lymphoma patients [14]. Lastly, exploring the unknown circulating microenvironment could lead to valuable information.

Circulating tumour cells, tumour-educated platelets, and extracellular vesicular DNA are under major investigation to see if they can overcome the weaknesses cfDNA/ctDNA faces and more studies are warranted to give definitive answers [15].

References

1. Bayly E, Nguyen V, Binek A, Piggin A, Baldwin K, et al. (2020) Validation of a modified pre-lysis sample preparation technique for flow cytometric minimal residual disease assessment in multiple myeloma, chronic lymphocytic leukaemia and B-non hodgkin lymphoma. Cytometry 98: 385-398.
2. Ubieto AIJ, Heredia Y, de la Rosa JM, Izquierdo AR (2020) Minimal residual disease monistoring from liquid biopsy by next generation sequencing in follicular lymphoma patients. Blood 136: 31-33.
3. Chase ML, Merryman R, Fisher DC, Jacobsen E, LaCasce A, et al. (2021) A prospective study of minimal residual disease in patients with diffuse large B-cell lymphoma using an Ig-NGS assay. Leuk Lymphoma 62: 478-481.
4. Ching T, Duncan ME, Newman-Eerkes T, McWhorter MME, Tracy JM, et al. (2020) Analytical evaluation of the clonoSEQ assay for establishing measurable(minimal) residual disease in acute lymphoblastic leukemia, chronic lymphocytic leukemia and multiple myeloma. BMC Cancer 20: 612.
5. Cheminant M, Derrieux C, Touzart A, Schmit S, Grenier A, et al. (2016) Minimal residual disease monitoring by 8-color flow cytometry in mantle cell lymphoma: An EU-MCL and LYSA study. Haematologica 101: 336-345.
6. Zhou Y, Chen H, Tao Y, Zhong Q, Shi Y (2021) Minimal residual disease and survival outcomes in patients with mantle cell lymphoma: a systematic review and meta-analysis. J Cancer 12: 553-561.
7. Karmali R, Abramson JS, Stephens DM, Barnes JA, Kaplan J, et al. (2020) Ibrutinib maintenance (I-M) following intensive induction in mantle cell lymphoma(MCL): Efficacy, safety and changes in minimal residual disease. Blood 136: 30-31.
8. Le Gouill S, Beldi-Ferchiou A, Alcantara M, Cacheux V, Safar V, et al. (2020) Molecular response after obinutuzumab plus high-dose cytarabine induction for transplant-eligible patients with untreated mantle cell lymphoma(LyMa-101): A phase 2 trial of the LYSA group. Lancet Haematology 7: e798-e807.
9. Wang YH, Chuang YK, Yang YH, Yu SC, Yang YT, et al. (2020) Next-generation sequencing minimal residual disease of mantle cell lymphoma in autologous stem cell grafts and its implication on tumour recurrence. Blood 136: 22-23.
10. Kumar A, Bantilan KS, Jacob AP, Park A, Schoninger SF, et al. (2021) Noninvasive monitoring of mantle cell lymphoma by immunoglobulin gene next-generation sequencing in phase 2 study of sequential chemo radio immunotherapy followed by autologous stem-cell rescue. Clin Lymphoma Myeloma Leuk 2152-2650.
11. Starza ID, De Novi LA, Cavalli M, Novelli N, Soscia R, et al. (2020) Immunoglobulin kappa deleting element rearrangements are candidate targets for minimal residual disease evaluation in mantle cell lymphoma. Hematological Oncology 38: 698-704.
12. Spina V, Bruscaggin A, Cuccao A, Martini M, Di Trani M, et al. (2018) Circulating tumour DNA revelas genetics, clonal evolution and residual disease in classical Hodgkin lymphoma. Blood.
13. Christiano S, Leal A, Phallen J, Fiksel J, Adleff V, et al. (2019) Genome-wide cell-free DNA fragmentation in patients with cancer. Nature 570: 385-389.
14. Wedge E, Hansen JW, Garde C, Asmar F, Tholstrup D, et al. (2017) Global hypomethylation is an independent prognostic factor in diffuse large B cell lymphoma. Am J Hematol 92: 689-694.
15. Cirillo M, Craig AFM, Borchmann S, Kurtz DM (2020) Liquid biopsy in lymphoma: Molecular methods and clinical applications. Cancer Treat Rev 91: 102106.