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 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.

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