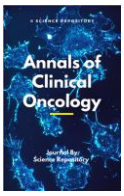

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Research Article

Is *TP53* mutation screening in Mantle Cell Lymphoma (MCL) ready for prime time?

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ABSTRACT

Mantle cell lymphoma (MCL) is a rare incurable subtype of B-cell lymphoma characterized by t(11;14)(q13;q32)-driven over expression of cyclin D1 [1]. MCL is associated with the highest degree of genomic instability of the B cell malignancies, and *TP53* mutation in particular confers a dismal prognosis in MCL with a reported incidence of 15-20 % (blastoid=29% vs Classical= 6%) [2, 3]. *TP53* mutation status is the only independent molecular marker that was able to improve the prognostic value of the Mantle cell lymphoma International Prognostic Index (MIPI) [4]. MCL Patients with a *TP53* mutation were significantly less likely to achieve a CR after first-line treatment and associated early relapse. The current standard of care, Chemo-immunotherapy with high-dose Cytarabine followed by autologous stem cell transplant (ASCT) (in eligible patient), although most patients prove ineligible, have failed to overcome the poor prognostic impact of *TP53* disruption [4]. Ibrutinib and Venetoclax (ABT-199) are two of the most active agents in the treatment of MCL, they have acceptable toxicity profiles and mainly are used in relapse setting. Pre-clinical models predict synergy between these novel drugs in combination. Patients who received Ibrutinib after an initial relapse had significantly longer PFS and OS than patients who received Ibrutinib after successive relapses probably related to selective advantage of resistant clone expansion [5]. In MCL, the attention should be move to the upfront treatment setting using these target therapies in high risk disease (*TP53* mutated) and elderly patients whom un-fit for chemo-immunotherapy approach and phase III clinical trial eagerly awaited to support this approach. Likewise, in chronic lymphocytic leukaemia (CLL) incorporating *TP53* mutation screening in routine practice prior commencing therapy is paramount in the era of novel effective therapies. Younger MCL patients with this genetic alteration should be considered for specific treatment using inhibitors for BCR, BCL2, *TP53*-independent pathways, the Anti-CD20 monoclonal antibodies either alone or in combination followed by allogeneic stem cell transplantation in the upfront setting. Chemo-free approach also to be considered for un-fit patients early in the disease course. Fit un-mutated *TP53* MCL Patients should be treated with chemo-immunotherapy with ASCT consolidation if eligible and anti CD20 monoclonal antibody maintenance therapy.

Background

Mantle cell lymphoma (MCL) is a rare subtype of B-cell lymphoma, accounting for 5-9% of all cases [1]. The pathogenic hallmark in MCL is the *t*(11;14) (q13;q32) translocation, with resultant over-expression of cyclin D1 causing cell cycle disruption [1, 2]. Classical MCL is believed to arise from naïve B cells that express SOX11, and typically involves lymph nodes and extra-nodal sites such as the gastrointestinal tract. More aggressive forms of MCL with blastoid or pleomorphic

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morphologies could represent disease progression. The other type of MCL develops from antigen-experienced SOX11-negative B-cells. It mainly involves the peripheral blood, bone marrow, and spleen and is often clinically indolent, not requiring treatment. Although significant improvements have been made in treatments, patients with acquisition of secondary genetic abnormalities, in particular *TP53* mutations have been associated with a very aggressive disease course [4]. Despite the prognostic impact of *TP53* disruption in MCL, screening for this genetic aberration has not been incorporated in routine practice in this disease. In this review, we would like to highlight the important of *TP53* disruption in MCL and propose incorporating this genetic defect screening in routine practice and we also suggest that patients with this defect should be treated with *TP53*-independent therapeutic approach in the era of novel therapies.

TP53 disruption & MCL

The median age at diagnosis is 65 years and the Mantle cell lymphoma International Prognostic Index (MIPI) is the most commonly used prognostic scoring system to predict which patients will have a more aggressive clinical course [6, 7]. *TP53* mutation status was found to be the only independent molecular marker that was able to improve the prognostic value of the MIPI [8]. In recent years, next-generation sequencing has led to comprehensive mutational characterization of MCL [9]. *TP53* mutations have recurrently demonstrated negative prognostic impact for the outcome of patients with MCL, and associated with inferior outcomes [9, 10]. MCL is associated with the highest degree of genomic instability of the B cell malignancies, and a large number of secondary chromosomal alterations have been described [11]. *TP53* mutation, in particular, which is 15-20% more common in the blastoid variant, confers a dismal prognosis in MCL with a median survival of 1.3 years versus 5.1 years for non-mutated disease (p=0.023) [12, 13]. In contrast, the prognostic relevance of 17p deletion in MCL is less clear, although several studies have indicated an association with shortened survival [14, 15].

MCL current standard of care

Considerable improvement in progression-free survival (PFS) has been achieved with current first-line chemo-immunotherapy regimes affording approximately 2 years disease-free, and dose-intensified therapy with high-dose cytarabine and autologous stem cell transplant (ASCT) consolidation in eligible patients achieving up to 5 years PFS [16, 17]. Non-randomized studies suggest that this approach is as effective as and less toxic than more intensive chemotherapy (Hyper-CVAD).These intensive frontline therapies are a double-edged sword considering deaths due to toxicity and the rate of secondary malignancies (solid tumours 9.4%, Myelodyspalstic syndromes (MDS)/leukaemia 3.1–6.2% [18, 19]. Maintenance rituximab appears to prolong PFS and evidence suggests it may improve OS in patients treated with R-CHOP, but not those treated with Bendamustine-Rituximab (BR) [20]. More recently, the adoption of rituximab as maintenance therapy following an autograft has been shown to significantly improve progression-free survival (PFS) and overall survival (OS) [21]. Allogeneic bone marrow transplant is the only curative option for this disease and produces long-term disease-free remissions for a round 30-40% patients. However, many patients are ineligible for bone marrow transplant consolidation.

MCL patients usually respond well to initial treatment, however these responses are not durable, and relapse is inevitable. Individual heterogeneity in clinical behaviour is still encountered, ranging from primary refractory disease to a PFS of 7 years [22]. Excluding transplant eligible patients as the majority of relapsed MCL patients will not be eligible for ASCT or Allo-SCT, the median survival after first relapse of MCL is 1–2 years. There is no standard second line chemotherapeutic regimen at relapse and generally produce short lived response. In patients who have not received ASCT as a part of the first line therapy, a consideration of ASCT or Allo-SCT in younger patient is a clinical option in eligible patients. ASCT consolidation appears to be more beneficial to those achieving first CR after not more than two lines of therapy [17].

With the advent of the oral Bruton tyrosine kinase (BTK) inhibitor, Ibrutinib is highly active in the majority of relapsed MCL patients, and the duration of response provides a window to plan and perform the allograft procedure in young fit patient. Ibrutinib with or without anti CD20 monoclonal antibodies is the most promising therapeutic option in relapsed disease. Responses are seen in approximately two-thirds of patients with the majority lasting more than one year and relatively well tolerated. A phase II study of Ibrutinib involving patients with relapsed or refractory MCL showed a best overall response rate of 68%, a rate of complete response of 21%, and a median progression-free survival of 13.9 months. A phase III trial showed a best overall response rate of 72%, a rate of complete response of 19%, and a median progression-free survival of 14.6 months [23, 24]. Different therapeutic options are available in relapsed disease, however, the choice of therapy will be influenced by age, performance status, co morbidities and initial therapy.

Target therapy in MCL

MCL is associated with the highest degree of genomic instability in the B-cell malignancy, and a large number of secondary chromosomal alterations have been described [11]. *TP53* mutation confers a dismal prognosis with inferior outcomes in MCL with a median survival of 1.3 years versus 5.1 years for non-mutated disease (p=0.023) [12]. Despite a significant improvement in disease outcomes achieved by the addition of Rituximab and high-dose Cytarabine to chemotherapy regimes, and consolidation with ASCT, which is considered to be the current standard of care for younger patients, this approach does not directly target *TP53* mutated MCL patients [18, 25].

Ibrutinib, Bruton's tyrosine kinase (BTK) inhibitor and Venetoclax, BCL2 inhibitor (ABT-199) are two of the most active agents in the treatment of chronic lymphocytic leukaemia (CLL) and MCL with an acceptable toxicity profil [26, 27]. In the phase III trial, Ibrutinib was superior to temsirolimus with regard to response rates, safety profile, and progression-free survival [26]. Common or serious side effects of Ibrutinib include bleeding due to platelet dysfunction diarrhoea, rash, and atrial fibrillation [24, 26, 28]. Resistance to Ibrutinib in mantle-cell lymphoma is often related to activating mutations in the nuclear factor κB (NF-κB) pathway whereas in resistant chronic lymphocytic leukaemia, mutations of BTK and PLCγ2 pathways are implicated [29-31].

Venetoclax is a BH3-mimetic agent that directly and specifically inhibits BCL2 inducing apoptosis in malignant cells when BCL2 is over expressed [32, 33]. In a phase 1 study, Venetoclax had greatest single-agent activity, among B-cell cancers, against chronic lymphocytic leukaemia and mantle-cell lymphoma both of which highly express BCL2 [27]. Across a range of doses in patients with relapsed or refractory MCL, a best overall response rate of 75% and a complete response rate of 21% were reported, with a median progression-free survival of 14 months [27]. Pre-clinical models predict synergy in these novel drugs in combination (Ibrutinib and Venetoclax) or Ibrutinib and Bortezomib) [24, 34]. This could possibly overcome drug refractoriness. Emerging evidences yielded perhaps less impressive results when Ibrutinib was used later in the disease course, of which partially related prior therapy inducing selective advantage of resistant clone expansion. Most recent phase II trial reported by Constantine et al 2018, suggest dual targeting of BTK and BCL2 with Ibrutinib and Venetoclax was consistent with improved outcomes in patients with mantle-cell lymphoma who had been predicted to have poor outcomes with current therapy with low toxicity profile [35]. Such an approach might challenge the current standard of care including the role of ASCT consolidation in this disease.

Mangament of *TP53* disruptet MCL

The available different therapeutic approaches in MCL, do not consider the high heterogeneity in the evolution of the disease in MCL patients. Although MIPI score has shown the capacity to clearly separate MCL patients into three groups with significantly different prognoses, it has no therapeutic decision impact on this disease [7]. Optimal management of MCL patient's harbouring *TP53* mutation is un-met clinical need, and alternative therapeutic approaches independent of the *TP53* pathway should be considered. In addition, unselected and ineffective therapy, a part of therapy related toxicities, this approach could also induce a resistant disease clone. These observations could partially explain the less impressive response to Ibrutinib mono-therapy when used in second line settings. The activity of targeted therapy in the relapse setting has prompted the development of front-line therapy trials in combination with chemo-immunotherapy [36, 37].

In contrast, screening for 17p deletion by FISH and *TP53* mutational status is now included in the routine assessment of chronic lymphocytic leukaemia (CLL) and more importantly, treatment algorithm are divided into two main groups depending on the presence or absence of *TP53* disruption [38]. The same has been observed in MCL, including disease heterogeneity, incidence and impact of *TP53* disruption on disease course and treatment outcome[12]. This is not altogether surprising, as conventional chemo-immunotherapy relies on an intact *TP53* pathway, it seems logical that the management of MCL patients might benefit from a similar approach. We believe MCL patients with mutant *TP53* status might be best treated upfront with specific therapy independent of the *TP53* pathway using, BCR inhibition, BCL2 Inhibitors or in combinations, +/- Allogeneic stem cell transplantation (if eligible) in the upfront setting. The use of Ibrutinib as a single agent in relapsed patients has yielded perhaps less impressive results than expected. Selection of treatment-resistant clones by the use of standard first-line therapies in patients with aberrant *TP53* has been hypothesized as a possible explanation for this [19]. This concern could be avoided by using Ibrutinib in combinations, with, for example BCL2 inhibitors (Venetoclax) as this combination has been proven to be effective in relapse setting [35]. In contrast, MCL patients without *TP53* mutation should be treated with chemo-immunotherapy and ASCT consolidation or rituximab maintenance as appropriate.

Conclusion

MCL continues to be challenging disease therapeutically despite recent significant developments. Our ability to further refine and integrate *TP53* mutation screening into our prognostic workup will improve our treatment algorithm allowing a more personalized approach to treat this disease with improved efficacy and minimal toxicity. We believe that MCL patients harbouring *TP53* mutations should be considered for alternative upfront therapies, and non-mutated cases should receive the current standard of care with chemo-immunotherapy and ASCT where suitable. A larger clinical trial urgently needed for this un-met clinical need to optimise up-front treatment approach in this sub-set of patients.

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