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Time-limited, chemotherapy-free treatment comes of age in chronic lymphocytic leukaemia

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The therapeutic landscape of chronic lymphocytic leukaemia (CLL) has been transformed by the advent of agents targeting Brutons' tyrosine kinase (Btk) and B-cell lymphoma 2 protein (BCL2)[1]. Pivotal studies demonstrated the superiority of such inhibitors for CLL treatment compared to chemoimmunotherapy [2-7]. Btk inhibitors such as ibrutinib and acalabrutinib are administered until progression or toxicity and although highly effective there is evidence of cardiovascular toxicities and mutations associated with resistance [2-5].

The BCL2 inhibitor venetoclax is likewise prescribed until progression but when combined with an anti-CD20 monoclonal antibody (mab) may be administered as time-limited (TL) therapy. The MURANO and CLL14 trials, were innovative studies of TL venetoclax and anti-CD20 mab regimens in CLL[6-7]. However, the results of TL venetoclax and anti-CD20 mab trials leave some unanswered questions: firstly, what are the relative merits of venetoclax and anti-CD20 mab TL regimens versus continuous ibrutinib and secondly, it is uncertain if the same outcomes could have been obtained with venetoclax monotherapy[8].

Approaches based on personalized minimal residual disease (MRD)-driven treatment have been explored in subsequent trials of chemo-free TL therapy investigating the combination of ibrutinib and venetoclax (I+V)[9-11]. The CLARITY study was the first proof-of-concept study that established the efficacy of I+V in patients with relapsed or refractory (R/R) CLL with MRD eradication as the primary endpoint [9]. These concepts were further developed in the CAPTIVATE study, that evaluated MRD-guided treatment discontinuation following completion of I+V in treatment-naïve CLL patients. In patients who achieved undetectable MRD (uMRD) and who subsequently discontinued I+V the 24-month progression-free survival (PFS) rates were similar in standard (95%) and genetically high-risk (84%) subgroups[10]. Notably, the CAPTIVATE trial established I+V as the first, all-oral, chemotherapy-free, MRD-guided, TL regimen for the upfront treatment of CLL.

The validity of the CAPTIVATE strategy is confirmed by the VISION/HO141 study in R/R CLL[12]. In this issue of the journal, Kater et al[12] present the primary analysis of this innovative study in which R/R patients with uMRD after 15 cycles I+V are randomized to continue ibrutinib monotherapy or I+V cessation . Trial participants who were MRD positive remained on ibrutinib monotherapy. The prespecified primary endpoint employed in this study assumed at least 75% of uMRD participants would remain free from progression 12 months after randomization. This endpoint was designed to allow for comparison with previous chemo-immunotherapy trials, however, the observed 96% rate of PFS in uMRD patients who stopped therapy compares favorably to the 84.9% PFS of participants who received TL venetoclax and anti-CD20 mab in the MURANO study. [6,12].

Due to a paucity of data on PFS outcomes following therapy with I+V, a subsequent confirmation of persistent uMRD should be sought in follow-up studies of personalized MRD-driven TL treatment [9-11]. Whilst the repeated demonstration of persistent uMRD status was mandatory for the discontinuation of therapy in the CAPTIVATE trial the same does not apply in the current study[10,12]. For the future use of TL targeted therapies outside of clinical trials the demonstration of sustained uMRD may be critical prior to the discontinuation of such therapy to reduce the risk of emergent drug-resistant mutations.

The safety analyses presented in the current study demonstrate that I+V did not lead to unexpected toxicities. The relatively low median cumulative illness rating scale of the patient cohort in the current study, may contribute to an overassessment of the favorable safety profile of I+V[12].

Kater et al[12] demonstrate that I+V reduces the so-called "compartment" effect observed when these compounds are used as monotherapy or in association with anti-CD20 mabs. I+V increases the chance of achieving a profound MRD response along with a significant shrinkage of lymph nodes when compared with venetoclax CD20 mab combinations which may have a lesser impact on nodal disease[6-7].

Finally, seven patients with uMRD who reverted to MRD positivity during observation were successfully retreated again with the combination of ibrutinib and venetoclax. Thus, MRD guided TL therapy for patients with R/R CLL may allow an intermittent treatment approach, possibly decreasing the likelihood of drug resistance and preserving the use of other classes of drugs for a later relapse of the CLL.

In conclusion, the paper by Kater et al.[12] supports the current transition in the CLL treatment paradigm from continuous to TL chemotherapy-free combination treatments[6-7,9-13]. Whilst the current study is underpowered to answer the question as to whether treatment discontinuation in uMRD patients will be associated with a difference in survival it represents an important step forward in our understanding about the deployment of personalized targeted therapies for patients with CLL.

CONFLICT OF INTERESTS

D JA reports personal fees and research funding from Roche Pharmaceuticals, honoraria from Gilead.

SM received honoraria from Janssen, Abbvie, and AstraZeneca, advisory board for Janssen, Abbvie, and AstraZeneca. Commercial relationship with companies is "**all outside of the submitted work".**

AUTHOR CONTRIBUTION

Authors equally contributed to the preparation of manuscript.

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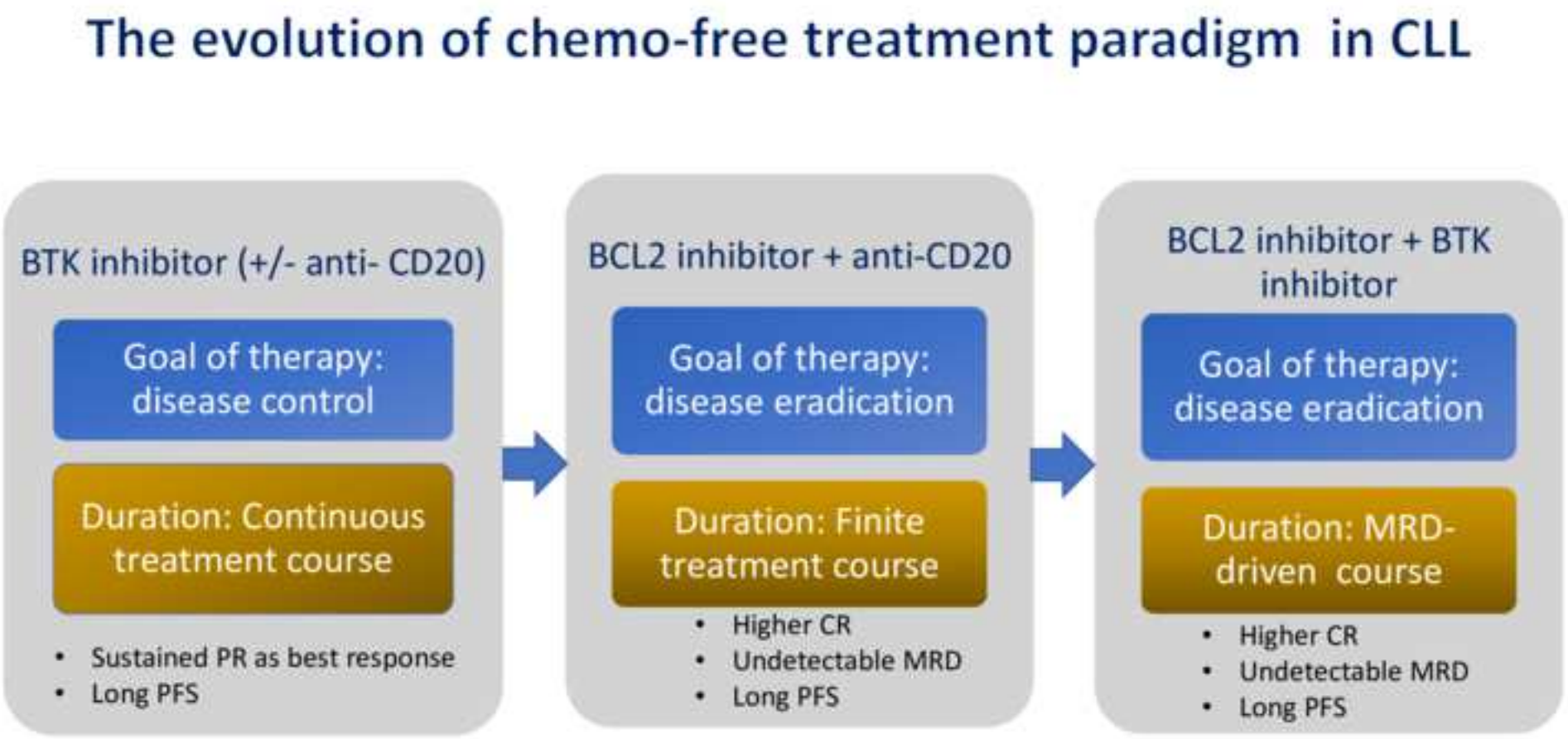
Figure



PR, Partial Response; CR, Complete Remission; MRD, Minimal Residual Disease; PFS, Progression-Free Survival;