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Transforming mantle cell lymphoma: the journey across eras

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In this issue of *Haematologica*, Jiang *et al.* report the evolution of overall survival (OS) and failure-free survival (FFS) following frontline therapy for mantle cell lymphoma (MCL) across different eras by pooling data from 6 phase III trials for treatment naïve and advanced stage MCL conducted from 1996 to 2020[1].

MCL has traditionally been considered an incurable disease. However, significant therapeutic advances since the 1990s have shaped current frontline standard-of-care approaches and improved patient outcomes. The evolution began in the 1990s with the GLSG1996 trial, which compared CHOP to MCP (mitoxantrone, chlorambucil, prednisone) and demonstrated higher overall response rates (ORR) with CHOP but no progression free survival (PFS) or OS benefit[2]. ORR, but not PFS, was further improved with the addition of rituximab to CHOP in the GLSG2000 trial[3]. However, it was not until the early 2000s that the comparison of autologous stem cell transplantation (ASCT) consolidation versus INF-α maintenance demonstrated a prolonged PFS with the inclusion of ASCT[4]. In the mid-2000s to 2010s, the incorporation of high-dose cytarabine into frontline induction therapy followed by ASCT was evaluated in the Nordic MCL1 and MCL2 protocols, as well as in the MCL Younger trial, and represented the first treatment strategies to demonstrate an OS benefit[5, 6]. For older patients not eligible for high-dose cytarabine and ASCT, the combination of bendamustine and rituximab demonstrated a superior PFS and improved tolerability compared with R-CHOP in the STIL NHL trial[7]. In recent years, rituximab maintenance following cytarabine-containing induction and ASCT was evaluated in the LYMA trial, which demonstrated an OS benefit and was subsequently widely adopted

and extrapolated to also be applied after other treatment strategies[8]. Subsequently, the incorporation of Bruton tyrosine kinase (BTK) inhibitors (Ibrutinib, Acalabrutinib) to frontline cytarabine containing induction (TRIANGLE) or bendamustine (SHINE, ECHO) further improved outcomes[9-11].

In their analysis, Jiang *et al*. pooled individual patient data from six pivotal randomized phase III trials in treatment-naïve MCL: GLSG1996, GLSG2000, European MCL Trial 1, MCL Younger, MCL Elderly, and TRIANGLE. Patients were categorised and regrouped according to the frontline treatment received into four eras: 1996–2000 (MCP, CHOP, R-CHOP), 2000–2004 (R-CHOP, CHOP-like + ASCT), 2004–2014 (R-CHOP, R-CHOP/R-DHAP + ASCT), and 2016–2020 (R-CHOP/R-DHAP + ASCT, IR-CHOP/R-DHAP + maintenance).

By aggregating these six landmark phase III trials, they analyzed outcomes of 2,541 patients, making this one of the largest cohorts to date for such comparisons. In younger patients (defined as under the age of 65 and suitable for high-dose chemotherapy), they demonstrated stepwise improvements in FFS and OS associated with the successive incorporation of rituximab, high-dose cytarabine, ASCT consolidation, rituximab maintenance, and ibrutinib. As observed in figure 1, improvements were observed across all time periods, with the most pronounced gains occurring between 2000 and 2005, an era characterized by the introduction of rituximab and ASCT, followed by sustained benefits thereafter. Interestingly, patients treated with the same regimen across different eras achieved comparable FFS and OS, suggesting that survival gains are primarily driven by evolving treatment strategies rather than temporal effects

or improvements in supportive care. However, when adjusted for MIPI risk groups and for patients with aggressive histology, high Ki-67, or p53 overexpression by immunohistochemistry, the survival benefit was attenuated. This attenuation was not observed among patients without high-risk features. In older patients (defined as over 65 or over 60 and not suitable for high dose chemotherapy), significant improvements in survival outcomes were seen with the addition of rituximab to induction therapy and the use of rituximab maintenance. However, it is important to highlight that the trials included in this analysis may not reflect the current practice, as no patient received bendamustine containing regimens and no patient above 65 years received frontline BTK inhibitor (as per TRIANGLE inclusion criteria).

As treatment strategies continue to evolve, the prospect of achieving a functional cure for MCL is becoming increasingly tangible, as observed in other indolent B-cell lymphoproliferative disorders where effective disease control may allow some patients to experience minimal impact on life expectancy[12]. Nevertheless, MCL remains a biologically heterogeneous disease, with a subset of patients presenting with highly aggressive forms that continue to represent a major unmet need as demonstrated in their analysis. CAR-T cell therapy has yielded durable responses in relapsed or refractory MCL, but without a clear plateau in survival curves and at the cost of significant toxicity and financial burden. Moreover, given the advanced median age at diagnosis, many patients are not candidates for currently approved CAR-T, emphasizing the need for effective, tolerable, and broadly accessible treatment options. Recently, the CD20×CD3 bispecific

antibody glofitamab monotherapy has shown encouraging activity, with impressive and durable responses in early-phase trials, and overall less toxicity than conventional chemotherapy or CAR T-cell therapy for patients with relapsed or refractory MCL[13]. As bispecific antibodies are now being evaluated in the frontline setting through new combination strategies, including specifically in patients with high-risk MCL, we are optimistic that outcomes will continue to improve in the years ahead.

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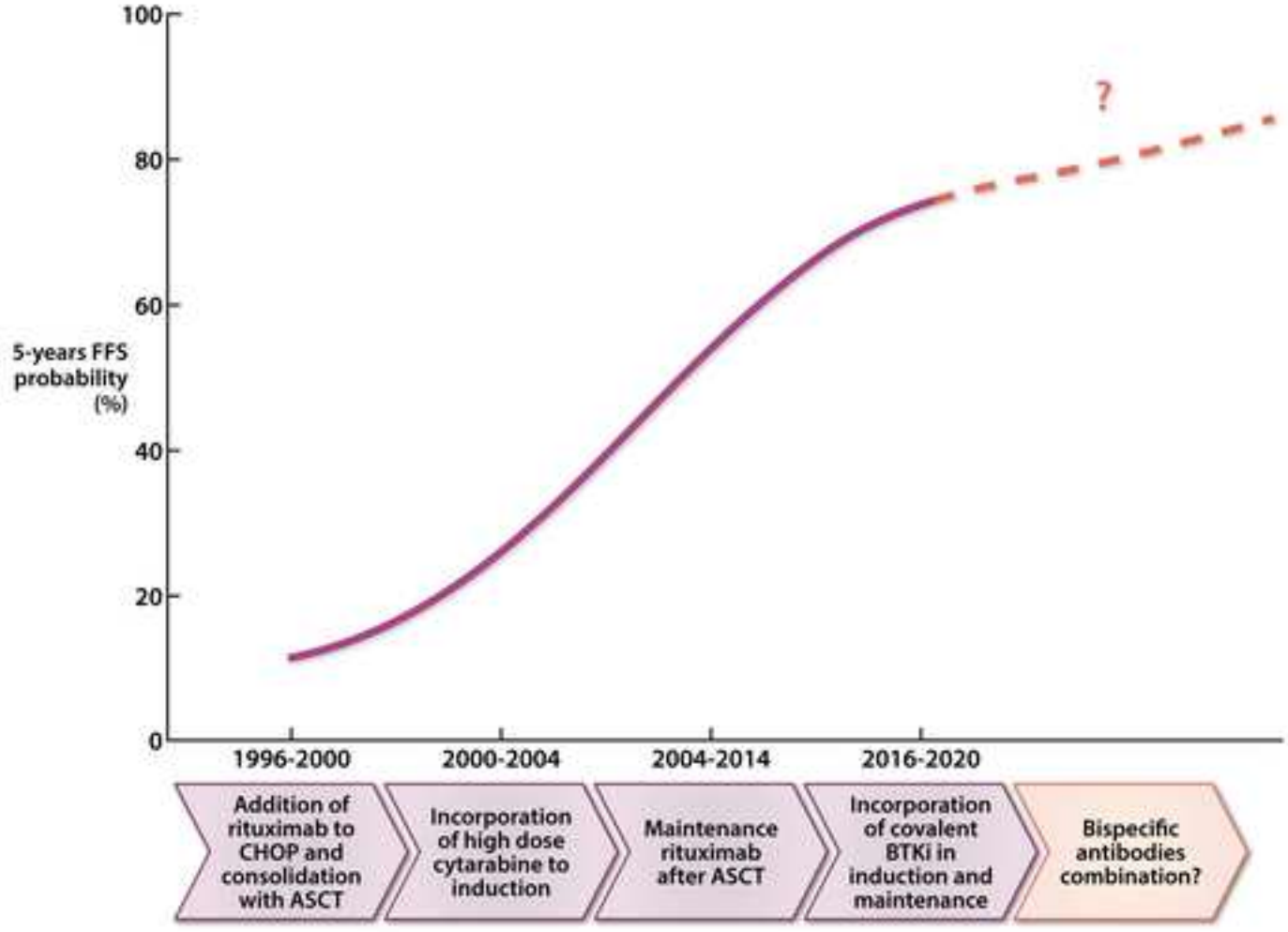
Legend to figure:

Progression in 5-year probability of failure free survival over time in patients with mantle cell lymphoma



ASCT: autologous stem cell transplant