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Review Article

Post ASH 2022: Mantle cell and low grade B-Cell Lymphomas

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ABSTRACT:

A summary of the most important data presented in the 2022 American Society of Hematology (ASH) Annual Meeting regarding treatment on low grade B-cell lymphomas and mantle cell lymphoma (MCL) is discussed in this review. Follicular lymphomas' treatment is rapidly changing with the introduction of novel agents both in first line and in relapsed/refractory setting. Among them, bispecific antibodies, such as mosunetuzumab, epcoritamab and odronextamab, have shown high response rates with long response duration in patients with relapsed/refractory disease and high-risk features, such as POD24 and multiple relapses, while the updated data on tisa-cel confirmed the long response duration of this CAR-T cell product with no new safety signals. Regarding MCL, the Bruton's tyrosine kinase inhibitors (BTKIs) have changed significantly the treatment landscape: The TRIANGLE trial confirmed the efficacy and safety of ibrutinib in first line treatment both as induction and maintenance therapy with or without ASCT, challenging the role of ASCT. The combination of acalabrutinib plus R2 has showed also promising results in 1st line treatment of MCL. In relapsed/refractory MCL, the results of the bispecific antibody Glofitamab were very promising even in high-risk patients with resistance to ibrutinib, while the activity and feasibility of venetoclax+R2 was also confirmed in a NORDIC study. Although most of these trials require longer follow-up in order to confirm their results, it is undoubtful that lymphoma treatment is entering in a new chemotherapy-free era with the novel agents being more efficacious and with a better toxicity profile. Bispecific antibodies, CAR-T cells, venetoclax and BTKIs are at the moment among the most promising ones.

KEY WORDS: *Follicular lymphoma, mante cell lymphoma, bispecific Abs, CAR-T cells, BTKIs*

INTRODUCTION

In the 2022 American Society of Hematology (ASH) Annual Meeting the results of several studies were presented regarding emerging therapies for indolent B-cell non-Hodgkin's lymphomas as well as mantle cell lymphoma. Below are short summaries of some of the data we thought were most interesting.

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As we will discuss in the following sections, novel therapies such as CD20 × CD3 T-cell-engaging bispecific monoclonal antibodies, are currently entering into the treatment landscape of B-cell lymphomas with great success, while in mantle cell lymphoma the role of autologous stem cell transplantation (ASCT) is disputed with the introduction of Bruton Tyrosine Kinase inhibitors (BTKis) in first-line treatment.

FOLLICULAR LYMPHOMAS

Bispecific Antibodies

Among low grade B-cell non-Hodgkin lymphomas (B-NHLs), the focus was mainly on follicular lymphomas, which will be further discussed.

Three bispecific antibodies confirmed their effectiveness in follicular lymphoma (FL) in the relapsed/refractory setting, namely mosunetuzumab, epcoritamab and odronextamab.

Mosunetuzumab has been approved as monotherapy for adult patients with relapsed or refractory (RR) FL after two or more lines of systemic therapy. A step-up dosing is followed in order to diminish the cytokine release syndrome (CRS). Mosunetuzumab is administered for 8 cycles for patients in complete response (CR), while patients with a partial response or stable disease after the 8th cycle, continue treatment up to 17 cycles. The safety and efficacy of mosunetuzumab has already been documented.[1,2] In the 2022 ASH meeting, an updated analysis from the pivotal phase II GO29781 study was presented which showed that mosunetuzumab continued to induce high and durable responses after a median follow-up of 28.3 months.[3] Ninety patients with RR FL and high-risk features [50% had progression of disease within 2 years (POD24), median of 3 previous treatments] participated in this study: 78% achieved an objective response after a median time of 1.4 months and 60% achieved a CR. After 24 months of achieving a CR, 62.7% of patients remained in remission, while the median progression- free survival (PFS) was 24 months. The median duration of response and the median duration of CR were not reached. A 12-month improvement in median PFS was observed with mosunetuzumab compared with the last prior therapy. No new safety issues were reported within a 10-month additional follow-up period. CRS events were experienced by 44% of patients and were predominately low grade and during first cycle.

The bispecific antibody *epcoritamab* has been combined with rituximab and lenalidomide (R^2) in patients with RR FL after at least one previous line of treatment, in a multicenter global phase 1/2 trial, called EPCORE™ NHL-2 trial.[4,5] Among efficacy-evaluable patients treated with subcutaneous epcoritamab in combination with R^2, 95% (63/66) achieved a response and 80% (53/66) achieved complete metabolic response (CMR). Most of the patients continued to respond until the latest assessment with a median follow up of 5.6 months. A manageable CRS occurrence was observed with only low-grade events, mainly following the first full dose, all of which resolved. The most common treatment-emergent adverse events (TEAEs) of any grade were neutropenia (47%) and CRS (43%).

Odronextamab is the third bispecific antibody tested in RR FL, which has shown significant efficacy. ELM-1 is an ongoing, open-label, multicenter phase 1 trial evaluating the safety and tolerability of odronextamab in patients with CD20+ B-cell malignancies after at least 2 previous therapies, including an anti-CD20 antibody and alkylating agent. Patients were treated with a step-up regimen of odronextamab in the first cycle prior to receiving the full dose of 80 mg. This step-up regimen was also modified during the trial to mitigate the risk of CRS. In the recent ASH meeting the results from the pivotal phase II study ELM-2 in RR patients with Grade I–IIIa FL were reported on 85 patients who had received a median of three previ- ous lines of therapy, demonstrating an 81% ORR with a median PFS of 20.2 months. A dosing step-up infusion protocol largely prevented CRS of Grade III or higher.[6]

Chimeric Antigen Receptor T- cells (CAR T-cells)

Besides bispecific antibodies, CAR T-cells are another effective treatment for RR FL, although logistic difficulties and the high cost remain significant barriers for being applied widely in the community setting. In the ASH 2022 meeting, Dreyling et al presented an update from the phase 2 ELARA trial, which showed durable responses with tisagenlecleucel in patients with RR FL.[7,8] In ELARA 97 patients were enrolled with 4 median lines of previous treatment and high-risk features. As it was previously reported, the ORR was 86% and the CR rate was 69%.[6] At a median follow-up time of 29 months, the median OS, PFS and duration of response were not reached, while the 2-year PFS was 57%.[7] No new safety signals were reported.

Other Targeted Therapies

The era of chemotherapy-fee treatment in lymphomas is rapidly expanding with the introduction of several targeted agents. The identification of EZH-2 mutation in ~20% of FL cases led to the development of an oral EZH-2 inhibitor, named tazemetostat. In a phase Ib study, 44 patients with RR FL who received ≥1 lines of therapy, received tazemetostat along with R^2, irrespectively of the EZH2 mutation status. As Salles et al presented, the ORR and CR rates were 98% and 51%, respectively, without any difference between mutated and unmutated cases. Moreover, responses were independent from rituximab refractoriness and POD24. At a median follow-up time of 11 months, 85% of the patients remained progression free. Neutropenia grade ≥3 was the most common and serious adverse event.[9]

The results of the phase III AUGMENT trial led to the approval of R^2 for patients with RR FL.[10] The 5-year survival and safety updates from this study presented at the recent ASH meeting, and confirmed the superiority of R^2 vs rituximab monotherapy in terms of PFS (27.6 vs 14.3 months, respectively), while median OS was not reached in both groups (83% vs 77%, respectively).[11] The safety profile also favored the combination arm, since the overall incidence of second primary malignances (SPMs) was lower in the R^2 arm.

First-Line Therapy

For low tumor burden, asymptomatic FL a watch-and-wait strategy is recommended.[12] In an international

randomized phase 3 trial conducted in UK, patients on watch and wait (WW) were compared to those on Rituximab with or without maintenance and followed for 12 years.[13] As it was presented at the ASH meeting, the rituximab groups were less likely to relapse: the median time to next treatment (TTNT) was 2.7 years for the WW group vs 9.9 for the 6 weekly rituximab group and not reached for those who received maintenance. However, no difference was noted in OS and transformation-free survival between the groups.[14] The question of whether to initiate treatment right away or watch and wait for signs of a need for therapy in patients with asymptomatic advanced-stage FL has no certain answer. This study implies that patient preference plays an important role and that a WW strategy is still a valid option.

MANTLE CELL LYMPHOMA

At the 64th ASH meeting extremely interesting and promising results on the treatment of mantle cell lym- phoma were presented, which may soon change clinical practice.

First-Line Therapy

One of the most important study presented in the plenary session is the TRIANGLE trial. In this three-arm randomized phase III trial, 870 previously untreated patients from 14 countries were assigned as follows: the control arm (A): standard-of-care induction chemoimmunotherapy (high-dose cytarabine-containing chemoimmunotherapy followed by ASCT and rituximab maintenance); the arm (A+I): induction chemoimmunotherapy plus ibrutinib and ASCT followed by 2 years of ibrutinib maintenance; and the third arm (I): induction chemoimmunotherapy with ibrutinib followed by 2 years of ibrutinib maintenance, without ASCT. Rituximab maintenance was allowed in all arms. Patients enrolled in TRIANGLE had stage II-IV MCL and were aged ≤65 years old. The response rates favored the ibrutinib-containing arms (CR: p=0.0203, ORR: p=0.0025). At a median follow-up of 31 months, the addition of ibrutinib to ASCT led to superior failure-free survival (FFS) vs ASCT: The 3-year FFS was 88% with ASCT+ibrutinib vs 72% without ibrutinib (p=0.0008), while the comparison of ibrutinib vs ASCT demonstrated higher 3-year FFS rates with ibrutinib (86% vs 72% on the ASCT arm) and was found to be noninferior to the current standard of ASCT after chemoimmunotherapy (p=0.9979). Median FFS was not reached in either arm. Regarding safety, more grade 3 or higher adverse events were observed during maintenance with the combination of ASCT and ibrutinib, suggesting probably that ibrutinib optimal use is as replacement rather than as combination to ASCT.[15] Overall, this study confirms the feasibility and activity of ibrutinib in the first-line treatment both as induction and maintenance therapy with or without ASCT. The current standard of care (ASCT) is not superior to the ibrutinib-containing regimen without ASCT, although longer follow-up is needed to better evaluate these results.

Another interesting chemotherapy-free approach in the first-line treatment of MCL includes the addition of acalabrutinib to rituximab and lenalidomide. In the phase II study presented at ASH 2022 researchers aimed to evaluate both the activity of the triplet combination, as well as the role of measurable residual disease (MRD) status in adjusting the treatment strategy in terms of intensity and duration.[16] High response rates were reported: ORR 100% and CR 83% after 12 cycles of treatment. At the time of analysis, 12 patients had completed 24 cycles of treatment and 9 of them with negative MRD proceeded to de-escalation to rituximab maintenance only. At 2 years after treatment de-escalation, 87% of the patients remain progression-free. Toxicity was manageable with no unexpected side effects. This study provides further insights on the role of novel biological agents in the treatment of a rather difficult disease, namely MCL. In addition it explores the feasibility of limiting the continuous and long-term use of these agents by using MRD as a treatment guiding strategy.

Relapsed/Refractory Disease

RR MCL remains an unmet need, since the prognosis is very poor. Indeed, for patients relapsing after a BTKi, the median survival is 6-10 months[17]. In this extremely dismal group of MCL patients some encouraging data have been provided recently. The bispecifc antibody glofitamab was shown to be effective with manageable toxicity.[18] At the recent ASH meeting the updated results of a phase I study of time-limited glofitamab in patients with RR MCL were reported.[19] Patients were pre-treated with Obinutuzumab (1000 mg or 2000 mg) 7 days prior to the first dose of glofitamab to mitigate the risk of CRS. Intravenous glofitamab step-up dosing was given on the first cycle, followed by a target dose of 16mg or 30 mg after 1000mg or 2000mg obinutuzumab, respectively, for up to 12 cycles. Overall 37 patients enrolled, 65% of which had been previously exposed to ibrutinib. After a median follow-up of 8 months, ORR and CR rates were 83.8% and 73%, respectively, across both obinutuzumab cohorts although the CR rate was higher with obinutuzumab 2000 mg (81% vs 62.5%). However, the most impressive, was that across both cohorts, the median time to achieving a CR was 51 days and an estimated 71.6% of patients with a CR remained in response at 9 months. The most common adverse events were CRS (75.7%) and neutropenia (40.5%), although the CRS rates were lower with the higher dose of obinutuzumab (66.7% vs 87.5%). Neurologic AEs

oc- curred in 15% of all patients although none discontinued treatment. Currently the treatment of choice for patients with R/R MCL, mainly for those relapsing or being refractory to BTKIs, include CART-cell therapy[20]. Brexu-cel, an anti-CD19 CAR T-cell therapy has been associated with high response rates (CR over 60%) and durable remissions[21]: After a median 32.3 months follow-up of the ZUMA-2 clinical trial, 39 percent of the trial's first 28 patients were still responding[22]. The high efficacy of CAR-T cells is unfortunately associated also with high toxicity: Severe toxicities include cytokine storm, macrophage activation syndrome, neurotoxicity, hemopoietic compromise and HLH. Based on the above data, Glofitamab may represent a good alternative treatment to CAR-T cells, since it is associated with similar activity, less toxicity and easier implementation.

Another interesting ongoing phase Ib/II Nordic trial (VALERIA) in RR MCL investigating the role of venetoclax in combination with R^2, was presented in the 64th ASH meeting. Fifteen out of the 59 enrolled patients had been previously exposed to a BTKi. VALERIA study is also exploring the feasibility of an MRD-guided treatment.[23] The ORR and CR rates were 63% and 49%, respectively (40% and 27%, respectively for the BTKi-treated patients). 59% of the patients stopped treatment after achieving MRD(-) CR and only 4 of them presented molecular relapse 12 and 14 months after the end of treatment, respectively, and restarted treatment. Toxicity was mainly hematological.

CONCLUSIONS

- Rituximab in low grade asymptomatic lymphoma may offer significant better TTNT compared to WW policy, without any impact on the response to next treatment, OS or risk of histologic transformation.
- Bispecific antibodies alone (mosunetuzumab, odronextamab) or in combination with (epcoritamab) other agents display great efficacy even in high risk RR FL patients.
- EZH2 inhibitors in combination with R^2 showed promising results both in EZH2 mutated and unmu- tated RR FL.
- In MCL, the introduction of ibrutinib in first line was associated with significant activity and acceptable toxicity even when combined with ASCT. The non-inferiority profile of ibrutinib compared to ASCT+ibrutinib supports the potential of an ASCT-sparing approach in younger patients with MCL.
- Several efficacious chemotherapy-free approaches were announced both in 1st line as well as in the RR setting in MCL, including combination of acalabrutinib with R^2 in 1st line and glofitamab in RR MCL.

Based on the above data it is obvious that the treatment landscape of FL and MCL is rapidly changing confirming the notion of a chemotherapy-free era of treatment.

Conflict of Interest: The author declares no conflict of interest.

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