Immunotherapy, Targeted Therapy, and Novel Approaches to Treating Lymphoma

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LYMPHOMA experts presented an insightful exploration of clinical trial data on immunotherapy and targeted therapeutics for diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL) during a joint symposium session chaired by Elizabeth Macintyre, Université Paris Cité; Institut Necker-Enfants Malades (INEM); Institut national de la santé et de la recherche médicale (Inserm); and Laboratory of Onco-Hematology, Assistance Publique-Hôpitaux de Paris, Hôpital Necker Enfants-Malades, Paris, France; and Robert Brodsky, Division of Hematology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

INTRODUCTION

There have been several advances in the treatment of DLBCL, FL, and MCL, with the approval of targeted therapies and the advent of immunotherapy and chemoimmunotherapy, as well as promising new drug targets on the horizon. However, whilst there have been major advances, this progress has not been easy, and future progress in improving lymphoma treatment and patient outcomes will require ongoing research and dedication. When discussing lymphoma treatment, John Gribben, Barts Cancer Institute, Queen Mary University of London, UK, and past President of the European Hematology Association (EHA), spotlighted the vast number of clinical trials investigating immunotherapies for treatment of DLBCL. Gribben explained how understanding of the failed immune mechanisms, as well as tumour cell biology and the microenvironment involved in lymphoma pathogenesis, could enable us to harness the immune system to develop immune-based therapies to treat lymphoma, highlighting monoclonal antibodies, immunomodulatory agents, and chimeric antigen receptor (CAR) T-cell therapy as some of the key areas of interest. Gribben stated that in order to alter clinical outcomes, successful therapies need to target the 'Achilles Heel' of the tumour. This will be the ongoing focus and challenge for lymphoma therapeutic research and development.

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IMMUNOTHERAPY

Whilst stating that chemotherapy remains the backbone of treating lymphoma, Gribben explored chemoimmunotherapy as one of the first major advances in lymphoma treatment, which has now overtaken chemotherapy as the standard of choice in treating lymphoma. Gribben highlighted the rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) regimen success, which has shown significantly improved overall survival (OS) when compared to CHOP due to the synergy between the anti-CD20 monoclonal antibody, rituximab, and traditional chemotherapy. Following on from this research and discovery, Gribben discussed how, more recently, clinical trials have been investigating the use of antibody-drug

conjugates to improve on R-CHOP outcomes, which have shown positive results. These discoveries signify the importance of enhancing immune-mediated effector mechanisms in treating lymphoma.

Lenalidomide

Gribben explored the use of the immunomodulatory agent lenalidomide in treating lymphoma. Lenalidomide acts by enhancing immune synapse formation to enable effective phosphotyrosine signalling to improve the T-cell response. This is important, as lymphoma cells have been found to induce gene defects in T-cells and natural killer cells, resulting in impaired function, such as impaired actin polymerisation, immune synapse formation, phosphotyrosine signalling, cytotoxicity, motility, as well as cytokine and chemokine production. The effect of lenalidomide on malignant lymphoma is, however, modest. Gribben also discussed clinical trial evidence that led to the licensing of lenalidomide for FL.

Chimeric Antigen Receptor T-Cell Therapy

CAR T-cell has been one of the major successes in treating lymphoma. Gribben highlighted some of the key clinical trials involving CAR T-cell therapies in relapsed/refractory lymphoma and the impact to patient outcomes, including the ZUMA-1 trial. ZUMA-1 has >5 years of data, and took place in patients with relapsed/refractory DLBCL who had received ≥2 lines of prior therapy. The findings showed that 43% were alive at 5 years. However, the aforementioned studies used to approve CAR T-cell therapy were Phase II and not randomised, due to a lack of other effective therapies available at the time. Gribben further explored how this led to comparative analysis studies of confounder-adjusted OS retrospectively reviewing overall and progression-free survival in standardised treatment historical cohorts, compared to outcomes with CAR T-cell therapy. These comparative studies have shown that CAR T-cells have made a major advance in this patient population, Gribben stated.

In terms of second-line therapy, Gribben discussed the ZUMA-7 study, which looked at axicabtagene ciloleucel versus standard of care, followed by autologous stem-cell transplant (ASCT), in patients with relapsed/refractory large B-cell lymphoma. The trial results showed that CAR T-cells outperformed ASCT in the patient cohort. However, Gribben did note that many of the patients in the cohort failed to make it to ASCT, and the inclusion criteria had to relapse within 1 year of receiving frontline therapy or having primary refractory disease, and would therefore be expected to do less well with ASCT. Furthermore, Gribben highlighted that the TRANSFORM study showed improved event-free survival in the CAR T-cell arm compared to standard of care. However, the BELINDA trial showed no difference in event-free survival between the CAR T-cell arm and standard of care arms. Gribben commented that this could be explained by the difficulty in getting CAR

T-cell therapy to patients in a timely manner in the context of aggressive disease. They also discussed comparative analysis studies performed in relapsed/refractory FL, as well as data from other trials investigating CAR T-cell therapy in relapsed/refractory FL and MCL.

Additionally, Gribben discussed that many patients undergoing CAR T-cell therapy would be unfit for ASCT. They spoke on real-world data, which showcased that CAR T-cell therapy can be delivered safely to patients deemed unfit for ASCT, and showed no difference in the incidence of CAR T-cell related toxicity or intensive care admission rates between ASCT-fit and ASCT-unfit patient cohorts.

Bispecific Antibodies

Gribben also discussed bispecific antibodies, spotlighting clinical trial data in relapsed/refractory DLBCL. They stated that responses have been impressive and durable when used as monotherapy. Further to this, bispecific antibodies can be effective in CAR T-cell failure. This is of importance, as it signifies that the mechanism by which tumours do not respond to CAR T-cell therapy is not due to intrinsic resistance to T-cell mediated killing.

TARGETED THERAPIES

Gilles Salles, Lymphoma Service Chief, Steven Greenberg Chair, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, USA, delivered a presentation on the progress and challenges associated with targeted therapies for MCL, FL, and DLBCL, with a focus on Bruton's tyrosine kinase inhibitors.

Bruton's Tyrosine Kinase Inhibitors

Salles explored the impact of ibrutinib, a Bruton's tyrosine kinase inhibitor (BTKi) on outcomes for relapsed/refractory MCL. Pooled analysis of clinical trial data showed that ibrutinib monotherapy resulted in improved patient outcomes and survival. Salles also discussed findings from SHINE, a Phase III randomised controlled trial comparing ibrutinib plus standard of care to standard of care plus placebo in the USA. The results showed improved median progression-free survival of 80.6 months versus 52.9 months, respectively. However, no difference was seen in OS between the two arms. Additionally, whilst more deaths due to disease progression occurred in the placebo arm, more deaths due to treatment-emergent adverse events, and more deaths during post-treatment follow-up that were not caused by disease progression, occurred in the ibrutinib arm. This was not felt to be sufficient to be a confirmatory trial of ibrutinib single agent.

Salles further discussed a European trial that evaluated the superiority of ibrutinib compared to the standard three cycles of R-CHOP and rituximab-dexamethasone, cytarabine, and cisplatin (R-DHAP) regimens followed by ASCT. The TRIANGLE trial used three arms: a control arm where patients received three cycles of R-CHP/R-DHAP and an ASCT; an experimental arm where patients received three cycles of R-CHOP+ibrutinib/R-DHAP, ASCT, and 2 years of ibrutinib maintenance; and another experimental arm where patients received three cycles of R-CHOP+ibrutinib/R-DHAP and 2 years of ibrutinib maintenance (no ASCT). Rituximab maintenance was added following national guidelines in all three trial arms. The results showed that ibrutinib had superiority over the control arm, and that there was no difference in outcome in patients treated with R-CHOP and R-DHAP plus ibrutinib in the presence or absence of ASCT (both experimental arms). Further work is required to clarify if the experimental arm without ASCT is superior to the control arm. The results of TRIANGLE have recently been implemented into the National Comprehensive Cancer Network (NCCN) guidelines for MCL.

Salles also discussed data from clinical trials investigating the use of BTKis as single agents, and in combination with other therapies in FL and MCL.

CHALLENGES AND FUTURE DIRECTIONS

During the presentation, Salles discussed the potential role for protein degraders, explaining that this novel class of therapeutics is being investigated for lymphoma treatment, and could have potential use in scenarios where resistance to other targeted therapies occurs, such as resistance to covalent BTKis.

Whilst this is an interesting area of research, and early results are becoming available, there is still further work to be done in this field.

Looking toward the future, Gribben discussed the successes of chemoimmunotherapy, CAR T-cell therapy, and the promise of bispecific antibodies as monotherapy. Bispecific antibodies are now being investigated for their potential role in combination therapy. Gribben stated: "We are in an era where we have seen immunotherapy markedly improve the outcome for our patients with lymphoma, and we're looking to see how we can improve it further." They commented on the potential for adding immunotherapies to targeted therapies to hopefully improve outcomes even further. Salles highlighted the potential for combination therapy and possibility for progression to chemotherapy-free regimens in the appropriate circumstances.

Regarding future challenges, Salles discussed that due to dysregulation of multiple oncogenic pathways, ensuring treatment is directed against the right target for the right lymphoma entity will remain an ongoing challenge. Additionally, the opportunities for therapeutic development will pose a challenge in a crowded market.

Despite the successes achieved thus far, Gribben commented that the future challenges will involve how to approach immune-mediated treatment for T-cell lymphomas. Salles discussed the ongoing need for translational research and collaboration between academia and industry, alongside examination of longer-term follow-up data.

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