The 4th LYSA meeting

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SUMMARY

The 4th edition of the LYSA meeting was organised by Professor Steven Legouill's team and held in Nantes from the 8th to 10th February, 2018. It was a real opportunity for the 500 participants to learn novelties on lymphoma and to be updated on ongoing clinical trials conducted by this cooperative group. All the presentations were outstanding and gave us new indications on how to better treat our patients in the near future.
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T-CELL LYMPHOMA

The session was opened by Philippe Gaulard, who summarised the history of the TENOMIC committee. A central biobank was created in 2008, and, since then, has collected biological material (FFPE biopsies and blood samples) from more than 1350 patients with T-cell lymphoma. In parallel, clinical data of the same patients were retrospectively collected, allowing a better understanding of the pathophysiology of every T-cell lymphoma subtype; this would enable the identification of new potential therapeutic targets.

François Lemonier reviewed the current peripheral T-cell lymphoma classification. He underlined the characteristics of the recently recognised 'follicular helper T-cell lymphoma', an overlap between angio-immunoblastic T-cell lymphoma and peripheral T-cell lymphoma (PTCL) not otherwise specified (NOS). He described different mutations involved in the lymphomagenesis that could be potential therapeutic targets. He also discussed the role of brentuximab vedotin in CD30-positive T-cell lymphomas and the efficacy of ALK inhibitors in patients with anaplastic large T-cell lymphoma. Targeting the altered JAK-STAT pathway is also under evaluation as a new therapy approach of T-cell malignancies.

Arnaud Jaccard discussed the guidelines for the management of nasal NK/T-cell lymphoma. The role of EBV infection in the pathogenesis, the clinical features and the staging work-up (including the use of ^{18}FDG TEP scans) were detailed. For localised disease, early applied radiotherapy, combined with gemcitabine, methotrexate, dexamethasone and L-asparaginase therapy, remains the cornerstone of first line treatment. For advanced disease, the same drugs are recommended followed by intensification and autologous stem cell transplantation. Other new drugs are emerging in the treatment of this type of lymphoma, such as daratumumab, brentuximab vedotin and anti-PD1.

Richard Delarue closed the session presenting ongoing and upcoming trials for T-cell lymphoma treatment including the TOTAL study (brentuximab vedotin and gemcitabine, for relapsing patients with CD30-positive T-cell lymphoma) and the ORACLE study (testing oral azacitidine in relapsing PTCLs with TFH phenotype).

HODGKIN DISEASE

The results of two phase III studies were presented. Andrea Galamini presented the final results of the ECHELON 1 trial, a phase III study comparing AVD-BV (brentuximab vedotin) with ABVD as first line treatment for newly diagnosed patients with advanced Hodgkin lymphoma. The final results showed a two years' modified progression free survival (PFS)

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advantage of 4.9% (82.1 versus 77.2%) in favour of the experimental arm. In terms of toxicity, AVD-BV is associated with an increased rate of haematological toxicity but manageable with systematic use of G-CSF and on the other hand a decreased rate of pulmonary toxicity.

Olivier Casasnovas presented the final results of the AHL 2011 study that highlighted the robustness of a PET-guided 'de-escalating' strategy (four cycles of ABVD instead of escBEACOPP) for patients with advanced Hodgkin lymphoma who achieved a complete metabolic response after two cycles of escBEACOPP. While PFS was similar in the two arms, haematological adverse events, febrile neutropenia and sepsis were significantly more frequent in the group of patients treated by six escBEACOPP cycles.

Julien Lazarovici presented the upcoming NIVINIHO trial testing the association of nivolumab and vinblastin for the treatment of unfit and elderly patients with previously untreated Hodgkin lymphoma. After an induction of six cycles of nivolumab, patients in complete metabolic response will receive a consolidation with additional eighteen cycles of nivolumab, while patients with less good response will receive an association of nivolumab and vinblastin.

Finally, Cedric Rossi presented the outcomes of 30 patients with refractory Hodgkin disease treated with anti-PD1 therapy, a treatment allowing the restauration of chemotherapy sensitivity and therefore giving a chance to reach sufficient response to perform allogeneic stem cell transplantation.

MANTLE CELL LYMPHOMA

Vincent Ribrag updated the recruitment status of MCL-R2 elderly, an international phase III clinical trial designed for elderly patients with previously untreated mantle cell lymphoma (MCL). In this study, patients are randomly assigned to receive three cycles of R-DHA28 alternated with three cycles of R-CHOP21 versus eight cycles of R-CHOP21 as induction therapy. There is a second randomisation for two years maintenance with rituximab alone versus rituximab and lenalidomide. To date, 344 patients have been recruited and 250 started maintenance. Interim analysis shows a post-induction minimal residual disease (MRD) negativity rate of 80% on peripheral blood and 59% on bone marrow. Therefore, Ribrag recommends that MRD status assessment should be performed on bone marrow rather than on peripheral blood due to its better sensitivity.

Steven Legouill detailed different ongoing ancillary studies using the database of the recently published LYMA study. Among them, information given by PET scans and MRD, genomic and epidemiologic features but also characteristics of refractory diseases will be analysed. He showed the impressive curve of inclusions in the LYMA101 study dedicated to young MCL patients. This trial evaluates four cycles of GA101-DHA-platinum salt followed by autologous stem cell transplantation conditioned by GA101-BEAM and, finally, maintenance by GA101 given every two months for three years. Moreover, an evaluation of the MRD is planned at the end of the maintenance, with monthly administration of GA101 in case of MRD positivity. In this setting of 'very high inclusion speed', discussions are ongoing to design future protocols in which the combination of new molecules, such as ibrutinib, ABT 199 or obinutuzumab will certainly be used.

A special lecture given by Martine Amiot was dedicated to the role of the BCL2 family in apoptosis, a review that was relevant at the time of venetoclax approval in Belgium.

Finally, Marion Alcantara reviewed the status of MRD evaluation, currently recommended by the ESMO guidelines in the setting of clinical trials but not yet used in routine. She illustrated the feasibility of the Droplet Digital PCR (ddPCR) used in the LYMA101 study cited above, where 73 patients underwent evaluation at baseline, 50 after induction treatment and 28 following autologous stem cell transplantation. Of the samples collected at the baseline, 80% was informative suggesting the feasibility of this approach.

INDOLENT AND FOLLICULAR LYMPHOMA

Splenic marginal zone lymphoma (sMZL) is characterised by specific clinical, immunophenotypic and genetic features different from other MZLs indicating that sMZL is a distinct clinicopathological entity. Alexandra Traverse presented available tools that can be used to confirm this diagnosis. Beside clinical features, histopathology, flow cytometry and cytogenetic characteristics, she illustrated the incidence of TP53, KLF2 and NOTCH2 mutations, three molecular abnormalities that can help pathologists confirm the diagnosis.

Cédric de Bazelaire, an interventional radiologist reported his experience in performing CT scan or ultrasound guided percutaneous spleen biopsy. He reported the results of a study performed in his centre that recruited 83 patients who underwent this procedure in the working out of splenomegaly, acytopaenia or for suspected haematological malignancy relapse. In this cohort, only two percent of the patients presented severe haemorrhage as a complication of the procedure. A diagnosis was made in 71%, and splenectomy could be avoided in 28% of the cases.

Anne-Ségolène Cottereau reviewed the place of ^{18}FDG PET/CT scan in the management of follicular lymphoma. It is now acknowledged that the use of PET/CT scan during follicular lymphoma management is associated with an improved survival, as published by Rai *et al*. last year. At initial staging, when transformation is suspected, PET/CT scans can guide

the biopsy on targeted lesions. The use of PET/CT scans can confirm a localised disease and support curative radiotherapy. An interim PET/CT scan has prognostic value but is not recommended routinely. At the end of treatment, persistence of PET/CT-avid lesions is associated with a lower prognosis and can serve to decide to prolong treatment. She also discussed the emerging prognostic value of total metabolic tumour volume performed at initial staging.

Gilles Salles presented the long-term follow-up results of the PRIMA study in which previously untreated patients with high tumour burden follicular lymphoma were treated with immuno-chemotherapy followed by maintenance rituximab. With a median follow-up of ten years, 80% of enrolled patients are alive and 50% have not required second line treatment. The expression of *cMYC* (>10%) and *p53* (>20%) was analysed in 253 patients of this cohort. In a multivariate analysis, the expression of *cMYC* was associated with a shorter PFS as reported by Danielle Canioni.

For treatment-naïve low-burden follicular lymphoma, the phase III randomised FLIRT study, comparing two routes of rituximab administration (sc. and iv.), is still ongoing in French centres. To date, 166 patients have been included. Unfortunately, despite the recent reimbursement of rituximab, this study will not be opened in Belgium.

Finally, for patients with indolent lymphomas requiring a second line treatment, the ambitious GATA project that combines obinituzimab, ABT 199 and the new anti-PD1 atezolizumab is now ongoing and has already recruited eleven patients.

DIFFUSE LARGE B-CELL LYMPHOMA

Two studies designed for patients in first line with localised disease are ongoing.

For patients younger than 60 years, without any risk factor of the age adjusted IPI, the LNH 09-1B study tests the pertinence of adapting the number of cycles of R-CHOP21 (four versus six) based on the early metabolic response.

The randomised SENIOR study evaluates the benefit of the addition of Revlimid to R-mini CHOP21 for elderly patients (80 years of age and over).

These two studies are now closed for inclusions. Beside primary objectives, ancillary studies are planned. Final analyses are expected for December 2020 for the LNH 09-1B and February 2019 for the SENIOR trial.

For young patients with one or more aaIPI risk factors, the Gained study compared two anti-CD20 antibodies, rituximab and obinutuzumab, in association with CHOP14 or the more intensive ACVBP14. Patients in complete metabolic response after two cycles of immuno-chemotherapy did not get a transplant. The results of this study confirm the relevance of an early PET-adapted strategy. Obinutuzumab did not improve PFS or overall survival and was associated with more serious haematological toxicities and more frequent infusion-related reactions than rituximab. Ancillary studies confirmed the identical overall survival in patients with ABC subtype and GCB subtype regardless of the technic used (Hans algorithm or NanoString assay). Ancillary studies showed as well a shorter PFS in case of BCL2 overexpression. The study was not designed to compare CHOP with ACVBP, therefore, the superiority of one regimen over the other remains questionable.

The association of R-CHOP21 with new molecules is being tested in various phase Ib-II studies for the treatment-enaïve diffuse large B-cell lymphomas (DLBCLs) arising in patients over 60 years of age. Tazemetostat (histone methyl transferase EZH2 inhibitor) and entospletinib (SYK inhibitor), both orally available, are under evaluation. LYSA is also involved in the international phase III POLARIX study that compares R-CHOP21 and the association of polatuzumab vedotin, a humanised monoclonal antibody targeting CD79b conjugated to auristatin, with R-CHP for previously untreated patients over 18 years of age.

David Maloney from Washington reviewed CAR T-cell-based therapies for patients with relapsed/refractory non-Hodgkin lymphoma (NHL). By enhancing adoptive T-cell immunity, this technique could revolutionise the prognosis of these patients. In the ZUMA 1 study, dedicated to patients with relapsed/refractory aggressive NHL, a treatment with axicabtagene ciloleucel resulted in an overall response rate of 82% with 54% rate of complete response. The main toxicities were neurological and related to cytokine release syndrome. Out of the 101 patients treated in the phase II, three toxic deaths were recorded.

In this setting of recurrent disease, André Bosly gave an overview of all the data presented at the last European Lymphoma Institute (ELI) meeting held in Lisbon last October, 2017. He underlined the poor outcome of refractory lymphomas. Similarly, Christian Gisselbrecht presented an update of the Scholar study, a meta-analysis of four European trials evaluating the treatment of patients with relapsed DLBCLs. This study was conducted with the aim to collect robust data able to convince European health authorities to give the reimbursement of CAR T-cells in our countries. With an overall response rate of 26% and a median overall survival of 6.6 months, he confirmed the real unmet need for this group of patients. Moreover, the prognosis of patients included in the Scholar study was poorer, with worse ECOG, than that of patients included in the above-cited ZUMA 1 study.

New drugs, such as selinexor (an *exportine* inhibitor), ibrutinib (a first class BTK inhibitor) and pixantrone (a topo-isomerase

KEY MESSAGES FOR CLINICAL PRACTICE

1. The sub-classification of different subtypes of T-cell lymphoma is better understood and specific targeted therapies are now being tested in clinical studies.
2. For Hodgkin lymphoma, the AHL 2011 study confirms the robustness of the 'PET-driven' strategy for patients with advanced disease. Nivolumab is under evaluation as first line treatment for unfit patients. In relapse setting, this drug can restore chemo-sensibility of the tumour.
3. For young patients with mantle cell lymphoma in first line treatment, the LYMA study strategy that consists in giving only four cycles of immuno-chemotherapy and that omits the use of TBI during stem cell transplantation conditioning, will probably become the new European standard of care for young patients in first line treatment.
4. For follicular lymphoma patients in first line treatment, long time follow-up of the PRIMA study confirms the efficacy of the regimen with a ten-year overall survival of 80%. For follicular lymphoma, the use of PET scan is essential throughout the treatment.
5. For patients with diffuse large B-cell lymphoma, a curative treatment, even after 80 years of age, remains the goal. After relapse, prognosis remains very poor. Before first line treatment, detection of patients at high risk of relapse is one of the current areas of research with the aim of testing new therapeutic modalities. For treatment-naïve patients, new drugs are being evaluated in combination with R-CHOP (polatuzumab vedotin, entospletinib, tazemetostat) and in combination with platinum-based chemotherapies (selinexor, ibrutinib, pixantrone, nivolumab) for patients with relapsed disease.
6. For primary central nervous system lymphoma, there is a trend to reduce the use of radiotherapy. New drugs are under evaluation (ibrutinib, lenalidomide, anti-PD1 and CAR T-cells).

II inhibitor), in association with platinum salt-based chemotherapy regimens, are under evaluation for patients with relapsed/refractory lymphoma who are candidates for intensification followed by autologous stem cell transplantation (ASCT).

For patients not eligible to ASCT (due to age or comorbidities) with recurrent B-cell and T-cell lymphomas, the international phase III randomised NIVEAU study is now recruiting. Its aim is to evaluate the benefit of adding nivolumab to the classical GEMOX regimen used in this population. This study is conducted in association with the HOVON, the German High-Grade Non-Hodgkin's Lymphoma (DSHNHL), the Czech Lymphoma Study Group (CLSG) and the Polish Lymphoma Research Group. This ambitious project will include 388 patients in 77 centres, aiming for an increase of 1-year PFS of 15%.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Carole Soussain overviewed the clinical practice guidelines for the treatment of primary central nervous system lymphoma. One of the main messages is the trend to reduce radiotherapy use in favour of chemotherapy or other systemic therapies.

For young patients, current trials are comparing ASCTsln with whole brain radiotherapy as a consolidation following induction therapy with high-dose methotrexate-based polychemotherapy.

For recurrent diseases, she discussed the new drugs used as a single agent or in association, such as ibrutinib, lenalidomide but also anti-PD1 and CAR T-cells.

Beside scientific presentations, this meeting gave us the opportunity to meet Pascal Bilbault, the new general director of the LYSARC and Bertrand Nadel, the director of the CALYM consortium.

During the meeting, elections of the members of the Administration and Scientific Committees were organised. Gilles Salles was re-elected President of the group. Franck Morschhauser, Steven Legouill and Camille Laurent reached the head of the Scientific Committee.

Most of the presentations are available on the LYSA website (*www.lysa-lymphoma.org*) for all members of LYSA.

Most of the trials mentioned above are open in Belgium. If you would like to know the participating centres, please download the 'Clin Trial Refer LYSA' application.