Highlights of the 13th International Conference on Malignant Lymphoma

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A lot of interesting data were presented at the 13th International Conference on Malignant Lymphoma in Lugano, Switzerland. The authors summarise below those presentations/abstracts they found relevant for daily practice, either now or in the near future.

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Hodgkin's lymphoma

The most important advances were reported in the treatment of Hodgkin's lymphoma.

Firstly, *P. Jonhson* (Southampton), presented the results of the RATHL study, designed to test whether interim ^{18}FDG PET-CT scanning could assess early chemotherapy response and guide subsequent treatment for patients with advanced classical Hodgkin's lymphoma (HL). Patients with newly diagnosed unfavourable localised or advanced stage HL were initially treated by two cycles of ABVD. After that, a ^{18}FDG PET-CT was performed to assess the early metabolic response, using the Deauville 5-point scale. Patients with negative ^{18}FDG-PET (score 1-3) were randomised to receive four complementary cycles of AVD with or without bleomycin. Patients with positive ^{18}FDG-PET (score 4-5) were treated with BEACOPP-14 or escBEACOPP. This study demonstrated, firstly, that bleomycin can be omitted for patients in early metabolic response (3-years PFS: 85.5% versus 84.5% and OS: 97% versus 97.5%, respectively for patients who received ABVD or AVD) with, as consequence, less pulmonary toxicity and, secondly, that radiotherapy can be omitted for this patient population in early metabolic complete remission. For patients with early ^{18}FDG-PET positive, no difference was observed between BEACOPP-14 and escBEACOPP (3-year PFS was 68% and OS 86%). (#008)

Secondly, the EORTC-LYSA-FIL intergroup presented the outcome of the early ^{18}FDG-PET-positive patients included in the H10 prospective randomised study (*Figure 1*). After two cycles of ABVD, patients with at least one unfavourable factor (more than fifty years of age, four or more involved nodal areas, ESR superior to 50 mm/1h without B symptom or superior to 30 mm/1h with B symptom, or a bulky mediastinum) were randomised between two additional courses of ABVD followed by 30 Gy Involved Node Radiotherapy (INRT) (standard arm) versus a more intensive chemotherapy treatment consisting of two cycles of escBEACOPP (escalation arm) also followed by 30 Gy INRT. ^{18}FDG-PET positive patients without any adverse factor (favourable group) randomised in the standard arm received one additional cycle of ABVD followed by 30 GY INRT and those randomised in the experimental arm benefited from two cycles of escBEACOPP followed by 30 GY INRT. With a median follow-up of 4.5 years, the authors demonstrate the negative impact of early ^{18}FDG-PET positivity on PFS and OS. Moreover, in the

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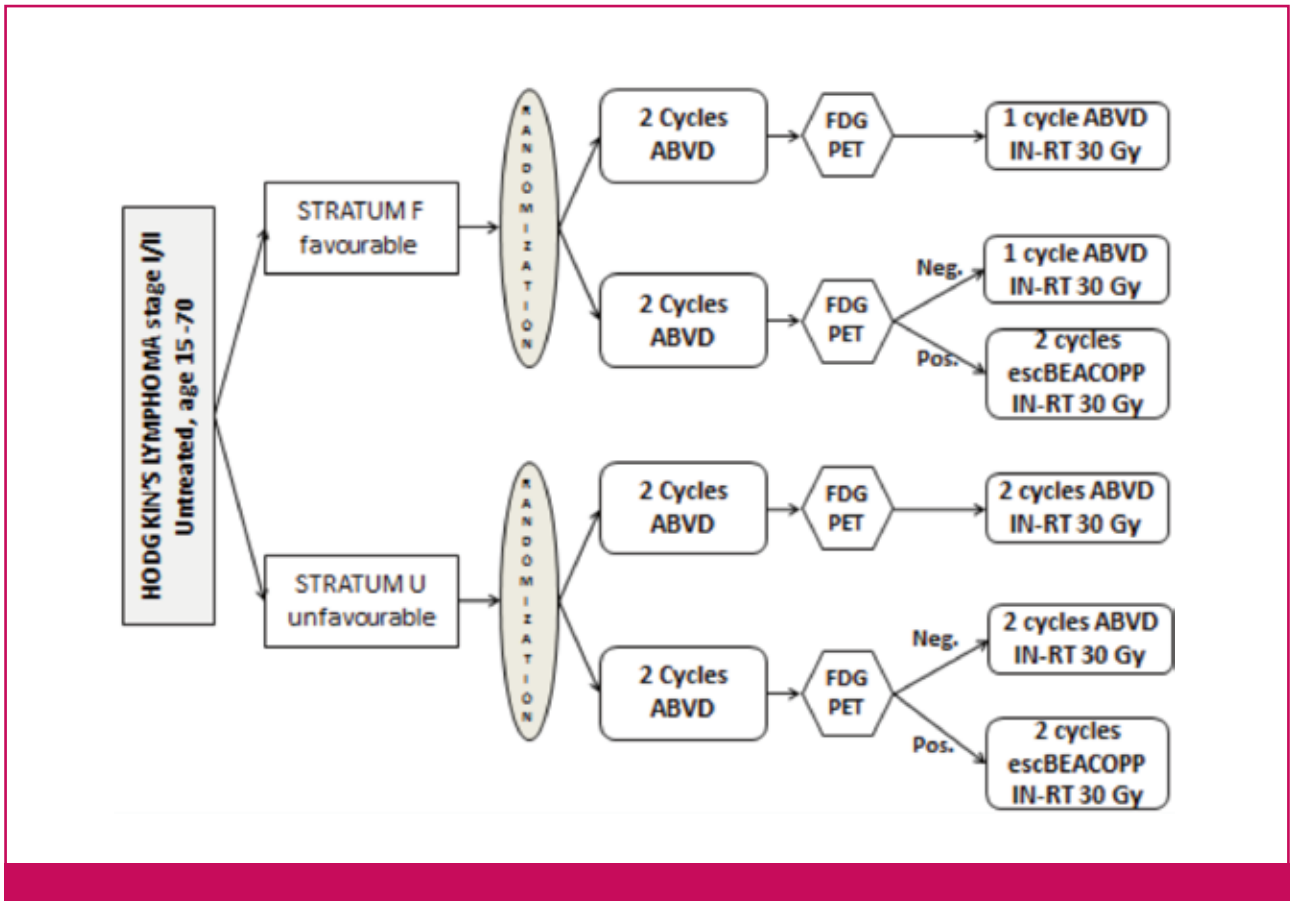

Figure 1. H10 study from the LYSA-FIL-EORTC Intergroup (#LBA1).
ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine; FDG PET: Fluoro Desoxy Glucose Positron Emission Tomography; IN-RT: Involved Node Radiotherapy; Gy: Grays. BEACOPP: Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone.

group of patients with early-PET remaining positive, an escalation treatment with escBEACOPP is associated with a five year PFS of 91% versus 77% for patients who did not receive escalation. Except for haematological toxicities, the escBEACOPP treatment was not more toxic. For patients with early ^{18}FDG-PET negativity, the final analyses confirmed the conclusions of the published interim analysis, i.e. they could not show the non-inferiority of the no-RT arm as compared to the standard combined modality treatment. (#LBA1)
Thirdly, the impressive results obtained with nivolumab (NIVO), a fully human IgG4 monoclonal PD-1 blocking antibody that is able to potentiate anti-tumour T-cell activity, already presented at the ASH meeting in December 2014, were updated and confirmed the very interesting potentiality of this drug in heavy pretreated Hodgkin's lymphoma with an overall response rate of 87%. Side-effects are rare and manageable. Among the 23 patients with HL included in the study, 20 responded. Out of them, ten discontinued NIVO, six (one CR and five PR) to undergo SCT, three for disease progression, one for toxicity (MDS, thrombocytopenia), and ten (seven PR and three CR) continue to respond. (#010)
Finally, brentuximab vedotin is now used in association. In first-line, coupled with AVD, it procures a CR rate of 93% for patients with non-bulky limited stage classical Hodgkin's lymphoma. In relapse, its association with bendamustine provides promising results. (# 87 & 90)

Diffuse large B-cell lymphomas

Two presentations focused on the place of radiotherapy in the treatment of localised diffuse large B-cell lymphomas (DLBCL), a topic that remains the subject of debate. Firstly, *D. Stephens* (US), presented an update of the worldwidely well-known SWOG S8736 phase III randomised study that was published in the NEJM in 1998 and had demonstrated, for patients with localised disease, the superiority in PFS and OS of a combined modality treatment (three cycles of CHOP followed by an involved field radiotherapy of 40-55 Gy) over eight

cycles of CHOP without radiotherapy. In the first publication, the median follow-up was 4.4 years. In 2001, during the ASH annual meeting, *Miller* already presented an update of this study and reported a higher number of relapse in the group of irradiated patients with no more advantage of the application of radiotherapy. To date, with a median follow-up of 17.7 years, 10- and 15-year PFS estimates in the combined modality arm (54% and 40%) are no different from the chemotherapy arm (55% and 41%; p=0.91), with continued relapses observed beyond five years in both arms. He concluded that extended survival data with over seventeen years of follow-up show similar PFS/OS with continuous treatment failure without a plateau in both arms. The addition of rituximab to the three cycles of CHOP does not seem to change the natural history of the disease. (#128)

J. Vargo (Pittsburgh) illustrated that, between 1998 and 2012, the use of consolidation radiotherapy after multi-agent chemotherapy in DLBCL was decreasing in the era of modern chemotherapy despite increased adoption of lower radiotherapy doses and modern radiation techniques. A retrospective study on 59,255 patients identified in the National Cancer Database was performed. Estimated 5- and 10-year overall survival was 79% and 59% for all patients, 75% and 55% for patients receiving multi-agent chemotherapy alone, and 82% and 64% for patients receiving combined modality therapy (p<0.0001). The author emphasises that abandonment of combined modality chemotherapy plus radiotherapy in favour of multi-agent chemotherapy alone negatively affects survival and should be cautioned but, it is important to note that the two groups of patients are not well-balanced in terms of prognostic factors and that the lymphomas of patients treated by chemotherapy alone are more advanced. Moreover, the use of rituximab was not generalised. (#129)

Follicular lymphomas

The risk of transformation of follicular lymphoma in the cohort of the PRIMA trial (six cycles of R-CHOP21 + 2R or eight cycles of R-CVP21 followed by rituximab maintenance once every two months for two years) was analysed by *C. Sarkosy* (Lyon). Among the 1,017 responding and randomised patients, a first recurrence was observed in 463 patients. The estimated annual transformation rate was 1.5%. Patients with histological transformation (HT) had significantly more frequently altered ECOG-PS, anaemia, high LDH level, B symptoms and high FLIPI score at diagnosis. However, initial regimen, quality of response to first-line therapy and R-maintenance did not impact the HT incidence. HT remains quite a rare event associated with poor outcome. The outcome of these patients can be improved by performing autologous stem cells transplantation. (#121)

The Follicular Lymphoma Analysis of Surrogacy (FLASH) group conducted a prospectively specified meta-analysis to evaluate whether treatment effect on the rate of patients who achieve complete remission at 30 months (CR30), an earlier endpoint, could accurately predict treatment effect on PFS. Thirteen randomised studies of first-line treatments in FL were eligible. Individual patient data (IPD) for 3,837 patients was accessible. Correlation of treatment effects on CR30 and on PFS was more marked in patients with more aggressive disease (stage IV or high FLIPI score). A minimum of 10% improvement in CR30 over a control rate of 50% predicted significant improvement in PFS. Correlation between treatment effect on CR30 and PFS in first-line chemo/immunotherapy FL trials was highly consistent across trial- and IPD-based surrogacy estimation methods and across sensitivity analyses. These data validate CR30 as a surrogate endpoint in first-line FL and support its use to accelerate drug development in this setting. (#122)

The primary results of the prospective phase III randomised GADOLIN study was reported by *B. Cheson* (Washington). This study compared the efficacy of six cycles of bendamustine 120mg/m^2 (days 1 and 2, cycles 1-6) alone to that of bendamustine 90 mg/m^2 (days 1 and 2, cycles 1-6) in combination with GA 101 1000 mg (days 1, 8 and 15 of cycle 1 and day 1 of cycles 2-6) for up to six 28-day cycles. Patients randomised in this latter arm received maintenance with GA 101 in monotherapy every two months for two years. With a median observation time of 20 months, the patients treated by bendamustine enjoyed a median PFS of 14.9 months. With 22 months of median follow up, the median PFS of patients who received immunochemotherapy was not reached [hazard ratio (HR) 0.55, 95% confidence interval (CI): 0.4-0.74; p=0.00011]. Patients treated by chemotherapy alone developed more grades 3 and 4 thrombocytopenia and anaemia. On the other hand, patients who benefited from immunochemotherapy presented more neutropenia and infusion-related reactions. (#123)

Chronic lymphocytic leukaemia

J. Bahlo (Cologne), presented a new pre-treatment prognostic index for CLL patients. After review of data

Table 1. CLL-IPI (#054).

Variable	Adverse factor	Coefficient	HR	Grading
TP53 (17p)	Deleted and/or mutated	1.442	4.2	4
IGHV status	Unmutated	0.941	2.6	2
B2M (mg/L)	> 3.5	0.665	2.0	2
Clinical stage	Binet B/C or Rai I-IV	0.499	1.6	1
Age	> 65 years	0.555	1.7	1

B_2M: B_2-Microglobulin; IGHV: immunoglobulin heavy chain variable region genes.

from eight phase III trials from France, Germany, UK, USA and Poland, including over 3,400 patients, five independent predictors for OS were identified: age (cut-off 65 yr), clinical stage (Binet A/Rai 0 versus Binet B-C/Rai I-IV), del(17p) and/or TP53 mutation, IGHV mutation status (MS) and serum β2-microglobulin (B2M) [cut-off 3.5 mg/L]. After applying weighted grading of the independent factors based on regression parameters, a prognostic index was derived separating four different risk groups [low (score 0-1), intermediate (score 2-3), high (score 4-6) and very high risk (score 7-10) (*Table 2*), with significantly different outcomes. This new prognostic model will probably be useful for current treatment recommendations. (#054)

P. Thornton (Ireland) reported an update of the phase III RESONATE™ study that compares ibrutinib (420 mg once daily) and ofatumumab for patients suffering from relapsed/refractory CLL. One hundred and ninety five patients received ibrutinib and 196 were treated by ofatumumab. In comparison with ofatumumab, treatment with ibrutinib procures higher ORR (90% versus 25%) and PFS (one year PFS: 84 versus 18%). Moreover, contrary to what is observed with treatment with ofatumumab, the efficacy of ibrutinib is independent of adverse baseline prognostic factors such as NOTCH1 mutations, complex karyotype, unmutated IGHV status, and 17p or 11q deletion. Most common grade 3/4 adverse events observed in the cohort of patients treated by ibrutinib were neutropaenia (18%), pneumonia (9%), thrombocytopaenia (6%), anaemia (6%), hypertension (6%) and atrial fibrillation (7%). (#055)

Mantle cell lymphoma

E. Hoster (Germany) presented a new prognostic model for patients suffering from a mantle-cells lymphoma. After review of the data of two studies from the European Mantle Cells Network (for young and elderly patients), it appears that the prognostic value of the combination of Ki67 serum level and MIPI is higher than those of the histological data such as blastoid cytology or diffuse growth pattern. By a simple combination of MIPI and Ki-67 index, using the previously established 30% cut-off, patients could be stratified into four groups with largely diverging PFS (5-year rates: 67%, 46%, 29% and 16%, $p<0.0001$) and OS (5-year rates: 85%, 72%, 43% and 17%, $p<0.0001$), independent of patient age and treatment strategy (*Figure 2*). (#058)

S. Legouil (Nantes) presented the results of the LYMA trial. In this study, patients younger than 66 years with untreated mantle cell lymphoma received four cycles of rituximab, high dose aracytine, cisplatine and dexamethasone (R-DHAP) followed, for responding patients, by intensification with autologous stem cells transplantation conditioned by BEAM. After that, patients were randomised between a watch-and-wait attitude versus a 3-year rituximab maintenance with an advantage for the patients receiving rituximab (3-year EFS: 88.1% versus 73.4%, $p=0.0057$). The advantage of the maintenance on OS is not significant. (#061)

Marginal zone lymphomas

C. Thieblemont (Paris) showed a new prognostic model focusing on MALT lymphomas generated from the dataset of the International Extra Nodal Study Group. The demographic, clinical and biological data of the 393 patients included in the IELSG-19 study and treated by chlorambucil, rituximab or rituximab-chlorambucil were collected and their impact on event, PFS and OS analysed. After application of a backward selection on data that were significant in univariate analysis, age

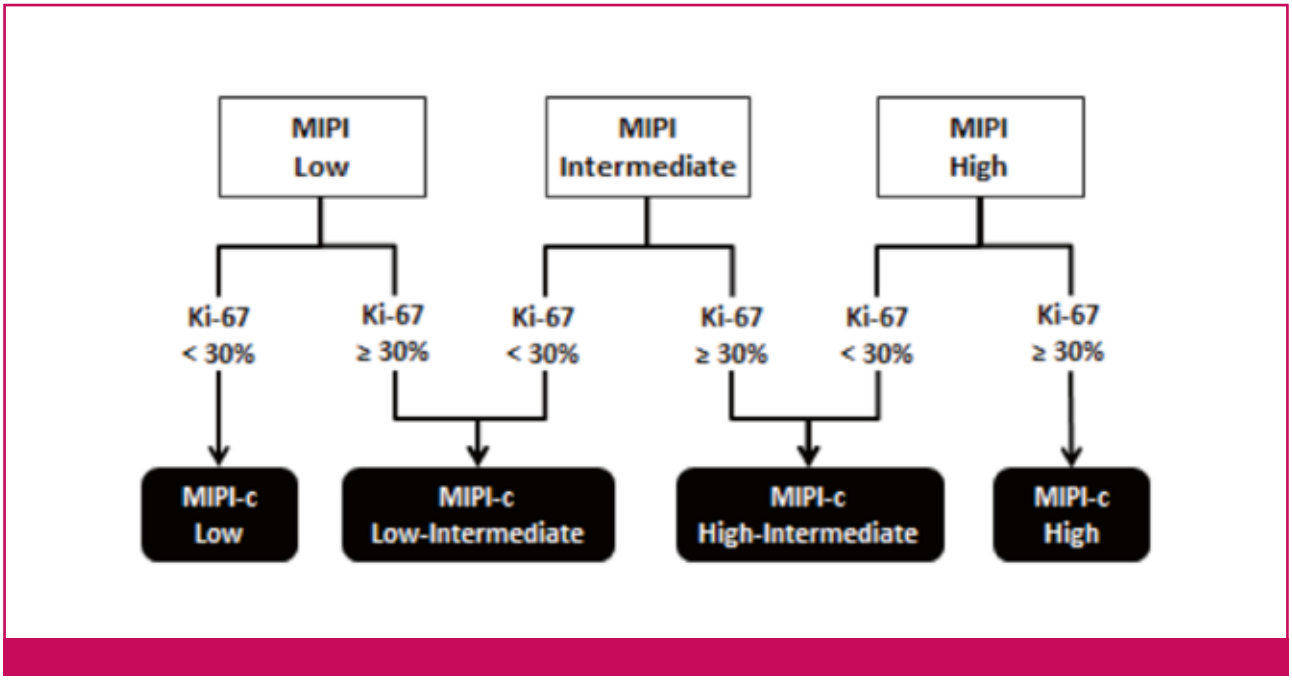

Figure 2. The Combined MIPI (MIPIc) (#058). MIPI: Mantle-Cells Prognostic Index.

>70 years, elevated LDH level and stage >2 remained significant in multivariate analysis. A prognostic score based on the presence of 0.1 or >1 of these three adverse factors was able to distinguish three risk groups with different 5-year EFS (72%, 58% and 26%; p<0.001), 5-year PFS (78%, 63% and 29%; p<0.001) and 5-year OS (99%, 92% and 74%; p<0.001). (#124)

CNS lymphomas

During the plenary session, *Dr Ferreri* (Milan) presented the results from the first randomisation of the International Extra Nodal Study Group (IELSG) 32. Firstly, this three arm international, multicentre, randomised study evaluated the effect of the addition of rituximab (375mg/m^2 on day -5 and 0) with, (arm C) or without (arm B) thiotepa (30 mg/m^2 on day 4) to the MATRIX regimen (methotrexate 3.5 g/m^2 on day 1 and cytarabine 2x2 gr/m^2 on days 2 and 3, arm A) in a cohort of 270 HIV-negative fit patients younger than 70 years suffering from primary CNS lymphoma. After four cycles, responding patients were further randomised to receive whole brain radiotherapy or autologous stem cells transplantation conditioned by BCNU and thiotepa. More grade 4 haematological toxicities were observed for patients receiving thiotepa without any increase of the infectious events. Arm C was significantly more active, with a CRR of 49%, an ORR of 87% and a 2-year PFS of 64%, a rate much better than that obtained with the addition of rituximab alone (52%) or without any new drug (34%). Second randomisation should be permitted to confirm the feasibility to perform high rates of successful ASC collection. (#009)

The German Cooperative PCNSL group reported preliminary results of the ongoing PRIMAIN study in which patients older than 65 years, suffering from untreated PCNS lymphoma, are treated by three cycles combining rituximab (375 mg/m^2 on days -6 [only cycle 1], 1, 15, and 29), methotrexate (3000 mg/m^2 on days 2, 16, and 30), procarbazine (60 mg/m^2 from days 2 to 11), and lomustine (110 mg/m^2 on day 2) followed by a maintenance phase of six cycles procarbazine (100mg/m^2 from day 1 to 5). In this frail population, lomustine appeared too toxic and was removed from the regimen. The authors demonstrated an overall response rate of 74%, a median PFS and OS of 11.5 and 22.7 months, respectively. Fifty four deaths were observed with six due to the treatment. (#134)

T-cell lymphomas

N. Schmitz (Hamburg) reported the results of pre-planned analysis of the Autologous or Allogenic Transplantation in T-cell lymphoma (AATT) randomised phase III study, designed for young patients with untreated peripheral T-cell lymphomas (PTCL). Patients were randomised to benefit, after four cycles of CHOP, from autologous or allogenic stem cells transplantation. Fifty eight out of the 104 enrolled patients were eligible for this interim analysis. Only 62% of patients completed treat-

Table 2. Causes of death of patients included in the AATT trial (#033).

	Autologous transplantation	Allogenic transplantation
Lymphoma progression	7	5
Salvage treatment	1	1
EBV + PTLD	0	1
Infection	0	4
Graft Versus Host Disease	0	2

EBV: Epstein Barr Virus; PTLD: Post-transplant lymphoproliferative disorder

ment as per protocol. Eleven patients were randomised to autoSCT but did not proceed to transplantation because of progressive disease or no response (n=8), infection (n=1) or change of histology (n=2). Fifteen patients (54%) randomised to alloSCT did not receive it due to progressive disease (n=10) or lack of a fully matched donor (n=5). The causes of death are mentioned in *Table 2*. In this small group of patients, no difference in OS was observed between the treatment groups. Moreover, over 30% of the patients randomised to ASCT or alloSCT did not make it to transplantation, mostly because of early lymphoma progression. In this situation, a conditional power calculation showed a low probability (<10%) that the primary endpoint could still be met and the investigators decided to close the study prematurely. (#033)

Another study focusing on the place of allogenic stem cell transplantation in T-cell lymphomas was presented by *A. Dodero* (Milan). He reported the long-term outcome (median follow-up of 60 months) of 72 patients affected by PTCL who underwent alloSCT at diagnosis (n=23) or for chemosensitive relapse (n=49) that have been enrolled into two transplantation protocols. Fifteen out of the 23 patients transplanted in first-line are alive in CR, four (17%) died of progressive disease (PD), three of non-relapse mortality (NRM) and one of myocardial infarction. In the group of patients transplanted after relapse, 31 of 49 (63%) patients are alive, 29 in CR, eleven (22%) died of PD, six of NRM and one of a second cancer. Patients who were transplanted in first CR did not have a significant advantage over patients who did after relapse (5-year PFS: 59% versus 43%, p=0.44; 5-year OS: 60% versus 58%, p=0.82, respectively). (#032)

Conclusion

In Hodgkin's lymphoma, the role of early PET is now clear for patients with localised or advanced diseases. For patients with localised diffuse large B-cell lymphoma, long-term follow-up of the SWOG S8736 demonstrates the non-superiority of chemoradiotherapy treatment over chemotherapy alone. In follicular lymphoma, the rituximab maintenance doesn't decrease the incidence of histological transformation. In the near future, the rate of CR at 30 months could replace PFS as the primary endpoint of clinical trials. The new CLL-IPI will probably be useful for treatment recommendations. In relapsed or refractory CLL, ibrutinib is associated with a better response rate and survival than ofatumumab. In mantle cell lymphoma, the combination of Ki67 index and MIPI has a better prognostic value than MIPI or Ki67 alone. In this disease, rituximab maintenance after autologous transplantation is associated with better PFS. In MALT lymphomas, age over 70, advanced stage and high LDH serum level are now recognised as important prognostic markers. For young patients suffering from CNS lymphoma, the addition of thiotepa and rituximab to cytarabine and methotrexate improves RR and PFS. For elderly patients, the association of procarbazine, methotrexate and rituximab is promising. Finally, for patients with untreated T-cell lymphoma, allogenic stem cell transplantation is probably too toxic and autologous transplantation is preferred.

References

1. 13th International Conference on Malignant Lymphoma meeting abstracts. Hematological Oncology. 2015 June 1;33(Suppl. 1).