Selected Update on Lymphoma from EHA 23 Congress

June 2018

This is a selection of lymphoma news or patient-related topics presented at the 23rd annual EHA congress in Stockholm (15 to 17 June 2018)

The summaries are taken from the abstracts and materials available on the EHA website (EHA learning center) with additional commentary and notes from Natacha Bolaños
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INTRODUCTION

At the 23rd EHA congress, held June 14-17 in Stockholm, and there were no less than 40 haematology disciplines covered, including lymphoma, through educational sessions, abstracts and posters. The Congress is important not only because it’s a source of information on breakthroughs in lymphoma care, but also because it brings together many of the patient groups that support the wellbeing of patients and their loved ones by providing updated information and guidance across the course of the disease.

Recent research findings presented at the scientific sessions are promising, but do not always lead to immediate changes for patients, or for clinical practice, so it is very challenging for us as advocates to know how to prioritise which information is the most essential and useful for our patients. In order to facilitate this for all of you as lymphoma patient organisations, we have prepared this summary that includes part of the contents that seemed to us to be more relevant to our community. The content is taken from the abstracts and materials available on the EHA Congress website with additional commentary and notes from myself.

For those who are interested in exploring more of the content from the congress, please visit the EHA Learning Centre on the EHA Congress website. On this platform, all of EHA’s educational resources and the 23rd annual EHA Congress content is offered in a user-friendly manner, including: congress webcasts; abstracts; e-posters; education books. In addition, new content such as expert interviews with leading haematologists are periodically uploaded to ensure users are aware of the latest developments on various haematological topics. The EHA Learning Centre is freely accessible to all EHA members, and advocates may easily become EHA guest members as at no cost:

- https://ehaweb.org/education/learning-center/
- https://learningcenter.ehaweb.org/

I hope you find this summary useful, especially to those who could not attend the congress.

Looking forward to hearing from you soon,

Natacha Bolaños
Regional Coordinator Europe
HODGKIN LYMPHOMA (HL)

The standard chemotherapy regimens for newly diagnosed and relapsed HL were introduced 20+ years ago. In the last 15 years, two major developments have fundamentally improved the management of HL.

- The introduction of PET scanning as a tool for determining early response to treatment, which has enabled a more individualised therapy management and allowed a reduction in treatment for some patients, providing a better balance between efficacy and late toxicity.
- Novel agents have greatly improved the treatment of relapsed and refractory disease, and are likely to be incorporated in earlier lines of therapy.

These developments are a consequence of a better understanding of the molecular biology and genetics of the disease and examples of successful translation of this understanding into clinical practice.

OPTIMISATION OF THE FIRST LINE TREATMENT IN CLASSICAL HODGKIN LYMPHOMA

First line treatment in classical HL has improved in many ways:

- The omission of radiation therapy in some early and advanced stage patients, which decreases long-term effects.
- The use of early positron-emission tomography (PET) scans after two treatment cycles allows clinicians to decrease treatment in good responders (with the subsequent reduction of late adverse effects) and to increase treatment only in those patients who need it (poor responders).
- Targeted therapies are now incorporated in first-line and may change therapeutic decisions.
- PET scans can be used to predict prognosis in classical HL.

Unfortunately, no biologic features or genetic markers have been shown to be helpful in therapeutic decisions but this may change in the next few years with new genomic data and testing for minimal residual disease. The focus now is moving toward maximising cure while minimising toxic effects.

EARLY STAGES

ABVD remains as the gold standard in the early stages of HL.

Positron-emission tomography (PET) scans should be used to guide a response-adapted approach:

- patients who have positive PET findings (active lymphoma) after chemotherapy receive radiotherapy
- patients with early (2 cycles) negative PET findings undergo no further treatment

The late toxic effects of radiotherapy are avoided in patients cured by chemotherapy, and long-term overall survival may be improved. This has been confirmed by two large randomized study with 91% progression free survival (PFS) in the favourable group who had 3 ABVD courses and 89.6% PFS in the unfavourable group who had 6 ABVD courses without radiation therapy.

It is important to note that the results of the trials that tried to compare progression free survival with or without radiation therapy are somewhat contradictory. One study defends the radiotherapy omission while the second failed to show non-inferiority of the omission of radiotherapy in the early-PET negative patients.

- From a clinical point of view, both these results confirm the best outcome for a combined modality which remains the standard of care.
- For the youngest patients with unfavourable stage II disease and extended lymph-node involvement or bulky disease, the omission of radiotherapy may be a good opportunity to avoid the long-term toxicity of radiotherapy.
ADVANCED STAGES

Since 2003, it has been shown that stage III/IV of classical Hodgkin Lymphoma may be treated with 6 courses of MOPP/ABV (mechloretamine, oncovin, prednisone, procarbazine, doxorubicin, bleomycin, and vinblastine) without radiotherapy if a complete remission is achieved after 4 cycles of treatment. This strategy decreases the risk of secondary solid cancers developing in the future due to the use of radiation therapy.

ABVD was shown as superior to MOP/ABV in regards to toxicity (mostly related to infertility and secondary cancers) but it could be improved. Higher survival rates are possible with escalated therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escBEACOPP), with higher-than-standard doses of etoposide, doxorubicin, and cyclophosphamide. This escalated regimen has been shown to yield higher progression-free survival rates than ABVD among previously untreated patients.

Trials in which ABVD and escBEACOPP have been directly compared have not shown a significant difference in overall survival, but a meta-analysis of several studies has suggested that the 5-year survival rate may be 5 to 10% points higher with escBEACOPP than with ABVD. More trials are needed to confirm these results, but due to new drugs for HL entering the market it is doubtful this will be pursued in the future.

This incremental difference in survivorship (escBEACOPP over ABVD) is achieved at the cost of significantly increased short-term and long-term toxic effects.

**EscBEACOPP (6 to 8 courses) carries the risk of:**
- permanent infertility
- prolonged fatigue
- myelodysplasia or acute leukaemia are more frequent (1.6 to 2 %) than with ABVD (<0.5 %)

**ABVD is generally associated with acceptable adverse-event rates, but it carries the risk of:**
- serious pulmonary toxic effects as a result of the bleomycin exposure
- cardiac toxicities, mostly in the elderly

Since the first studies comparing BEACOPP to ABVD, two different options have been proposed based on early PET evaluation:

1. **Begin treatment with ABVD and to increase in early positive PET (active cancer) with escBEACOPP and to decrease treatment in the negative PET population by omitting bleomycin.** Results for the 85% of patients with early negative PET are excellent with a 3-year PFS at 85%; with similar results for patients receiving and those who did not receive bleomycin after response.

2. **Begin treatment with escBEACOP and decrease to ABVD x 4 courses in early PET2 negative (87%).** This option has randomly been compared to 6 escBEACOPP and both show a 5-year PFS at 86%.

- The two series are not comparable in term of advanced patients, with 40% stage II in the first one versus only 10% in the second.
- Both strategies can be applied but young and advanced patients (e.g. with bulky disease) benefit more from escBEACOPP early in their disease course.
- Treatment with only 2 escBEACOPP cycles reduces dramatically the toxicities related to this regimen compared to when it is given over 6 cycles.
- The recent HD18 study from the German Hodgkin Study Group (GHSG) has confirmed no need for consolidation radiotherapy in post-chemo PET-negative patients and the possibility of limiting the number of escBEACOPP treatment cycles to four without loss of tumour control.

Another approach is to **omit procarbazine and replace it with dacarbazine**, as in the paediatric protocols; with this substitution the rate of infertility and secondary cancers is diminished.
TARGETED THERAPIES

CD30 is a surface antigen expressed on Reed–Sternberg cells in classical Hodgkin Lymphoma (cHL). Brentuximab vedotin is an antibody-drug conjugate used to treat relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL). It selectively targets tumour cells expressing the CD30 antigen.

This innovative treatment was approved in 2011 for the treatment of cHL after failure of autologous stem-cell transplantation or after two or more multi-agent chemotherapy regimens in patients who are not candidates for transplantation. A previous phase 1, dose-escalation trial involving patients with advanced Hodgkin lymphoma evaluated the use of frontline Brentuximab vedotin combined with doxorubicin, vinblastine, and dacarbazine (A+AVD) and showed it had an acceptable side-effect profile in the absence of bleomycin.

On the basis of these findings, ECHELON-1, a large, international, open-label, randomised, multi-centre, phase 3 trial was conducted to compare A+AVD with ABVD as frontline therapy in patients with stage III or IV cHL. The results from this large international study have been released. The study included 1334 patients and showed a 5% benefit of the experimental arm with Brentuximab vedotin. In intent to treat, the 2-yr progression free survival was 82%. This study is difficult to compare to previous studies for many reasons:

1. inclusion criteria regarding age and stage are not the same
2. the primary endpoint was a modified progression free survival taking into account progression and death but also detection of a response that was less than complete at the end of primary chemotherapy (Deauville score of 3, 4, or 5 on a PET scan), followed by the delivery of subsequent anticancer therapy. This criterion is difficult to compare and now most PET-guided studies consider that a Deauville score of 3 indicates a complete remission.
3. Echelon1 was not a PET-guided study and cannot be compared to the more recent studies based on early PET2 evaluation.

Brentuximab vedotin has also been used with BEACOPP replacing both vincristine and bleomycin (BrECAP). Also, procarbazine has been replaced by dacarbazine and prednisone by dexamethasone to give the BrECAADD regimen. Both regimens have shown high response rates in a phase II study.

Classical HL is characterised by malignant Hodgkin Reed-Sternberg (HRS) cells dispersed within an extensive inflammatory/immune cell infiltrate. HRS cells frequently harbour alterations in chromosome 9p24.1, leading to overexpression of programmed death-ligand 1 (PD-L1) and PDL2, ligands of the programmed death 1 (PD-1) immune checkpoint receptor.

For these reasons, relapsed/refractory HL patients have been treated with nivolumab and pembrolizumab with high response rates from 60 to 80% in phase 1 trials. They are now used in first relapse and may be incorporated in first line in association with AVD.
VITAMIN D DEFICIENCY AND REDUCED HODGKIN LYMPHOMA SURVIVAL

Vitamin D deficiency at baseline (in patients with Hodgkin lymphoma) is strongly associated with lower rates of progression-free survival (PFS) and overall survival (OS), independently of key factors that include tumour mass, patients’ clinical condition, and the type of treatment received, according to new research.

What really matters is that **Vitamin D deficiency is a clinically modifiable risk factor** for PFS and OS across multiple studies with long-term follow-up.

The data comes from the German Hodgkin Study Group (GHSG) HD7, HD8, and HD9 clinical trials. Disease status ranged from favourable to advanced. An enriched analysis was compiled using data on the patients’ pre-treatment serum samples and their documented progression or relapse.

The final analysis included 351 patients:
- 233 were relapse-free
- 118 relapsed

Among all patients:
- 175 were determined to be vitamin D deficient*
- 83 were determined to have insufficient levels of vitamin D*
- 93 had sufficient levels*

*Based on guidelines from the Food and Nutrition Board of the Institute of Medicine.
- less than 30 nmol/L deficient
- 30 to 50 nmol/L insufficient
- 50 nmol/L or higher sufficient

Patients who experienced progression or relapse were found to have significantly lower median baseline vitamin D levels than those who were relapse free (21.4 vs 35.5 nmol/L). They were also more likely to be deficient in vitamin D (68% vs 41%; P < .0001). Effects were similar across all treatment arms.

The analysis showed **vitamin D deficiency to be strongly associated with lower PFS** (hazard ratio [HR], 2.13; 95% confidence interval [CI], 1.84 - 2.48; P < .0001) over a median observation time of 156 months.

**In terms of overall survival (OS), vitamin D-deficient patients also had a significantly higher risk for death** (HR, 1.82; 95% CI, 1.53 - 2.15; P < .0001), after adjustments, over a median observation time of 192 months in the weighted analysis.

**Hodgkin lymphoma was the cause of death of 24 patients (38%) who were vitamin D deficient**, compared to only four patients (22%) whose level of vitamin D was insufficient, and three patients (18%) who had sufficient levels of vitamin D.

In addition, total deaths of all causes were higher in patients who were vitamin D deficient (n = 63; 36%) compared to those whose levels were insufficient (n = 18; 22%) or sufficient (n = 17; 18%).

**PET-GUIDED DE-ESCALATION EFFECTIVE IN ADVANCED HODGKIN LYMPHOMA**

PET can be safely used to guide treatment in patients with untreated advanced-stage classical Hodgkin lymphoma after 2 cycles of upfront de-escalated BEACOPP (BEAesc).

**Phase III LYSA (Lymphoma Study Association in France) randomised study driven by PET, a total of 823 patients were enrolled.** The purpose of this study was to evaluate the strategy of escalated treatment in patients with advanced Hodgkin lymphoma. Investigators aimed to evaluate whether de-escalation of BEACOPP in patients with advanced Hodgkin lymphoma would be beneficial without diminishing disease control. Patients received 2 cycles of BEAesc in order to obtain disease control (similar to 6 cycles of BEAesc with lower toxicity). PET positivity (cancer activity) in the standard arm and the experimental arm were comparable (12% vs 13%).

<table>
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<th>Experimental arm</th>
<th>Standard arm</th>
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<tr>
<td>410 patients</td>
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<tr>
<td>PET2-negative patients received 4 cycles of ABVD after 2 BEAesc cycles</td>
<td>no PET-driven strategy</td>
</tr>
<tr>
<td>PET2-positive patients received 4 cycles of BEAesc after the initial 2 cycles of BEAesc</td>
<td>all patients received the same therapy, comprised of 6 cycles of BEAesc</td>
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<td>5-year progression-free survival (PFS) was 85.7%</td>
<td>5-year PFS in the standard arm (86.2%)</td>
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<td>Toxicity was lower in patients who received 2 cycles of BEAesc plus 4 cycles of ABVD</td>
<td>Toxicity was higher in patients who received 6 cycles of BEAesc</td>
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<td>The most frequent grade ≥3 AEs were</td>
<td>The most frequent grade ≥3 AEs were</td>
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<tr>
<td>- anaemia (2%)</td>
<td>- anaemia (11%)</td>
</tr>
<tr>
<td>- leukopenia (74%)</td>
<td>- leukopenia (85%)</td>
</tr>
<tr>
<td>- thrombocytopenia (15%)</td>
<td>- thrombocytopenia (44%)</td>
</tr>
<tr>
<td>- sepsis (3%)</td>
<td>- sepsis (7%)</td>
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<td>102 serious treatment-related AEs were reported in 62 (17%) patients in the experimental arm.</td>
<td>204 serious treatment-related AEs were reported in 119 (26%) of patients in the standard arm.</td>
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<td>2 deaths were reported</td>
<td>6 deaths were reported</td>
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The disease control was similar in both arms, and PFS was quite satisfactory with a 5-year PFS of 85.7% in the experimental arm. The overall survival was also similar in both arms.

Serious adverse events (AEs) were reported in both arms, although the rates of these AEs were notably lower in the experimental arm. The most frequent grade ≥3 AEs were anaemia (11% vs 2%), leukopenia (85% vs 74%), thrombocytopenia (44% vs 15%), and sepsis (7% vs 3%), in the standard arm and experimental arm respectively. Of the 823 patients enrolled, 204 serious treatment-related AEs were reported in 119 (26%) of patients in the standard arm, and 102 serious treatment-related AEs were reported in 62 (17%) patients in the experimental arm. Subsequently, there were 6 deaths in the standard arm and 2 in the experimental arm.

The estimated 4-year PFS at a median follow-up of 50 months in the PET-driven experimental arm was comparable to the standard arm (87.1% vs 87.4%). In the overall population, PET2-positive patients had a significantly lower 4-year PFS compared with patients who were PET2-negative (70.7% vs 90.4%; P < .0001). This was also true in both randomised arms (75.1% vs 94% and 70.8% vs 91.6% in the standard and PET-driven arms, respectively; P < .0001 for both). The OS was similar in both arms.

The study shows:

- PET performed after 2 cycles of BEAesc can be safely used to guide subsequent treatment and supports the response-adapted strategy of delivering 4 cycles of ABVD for patients with negative PET2.
The PET scan was analysed centrally in real-time, which makes this approach quite easy to implement in clinical practice.

- Treatment can be reduced in 84% of patients without impairing the disease control, allowing a significant reduction in treatment-related toxicity in most patients.
- This approach has the potential to become the new standard of treatment, providing similar patient outcomes compared with standard BEACOPP treatment.
- The findings showed a higher risk of disease progression for patients who were PET-positive after 2 cycles of BEAesc.
- It has been also suggested that these results should encourage the field to develop new treatment options for patients with advanced-stage classical Hodgkin lymphoma who are PET2-positive.

**RELAPSED/REFRACTORY HODGKIN LYMPHOMA**

The majority of patients with HL can expect to be cured from their disease by frontline therapy, but up to 20% of patients who achieve a treatment response will subsequently relapse after completion of treatment.

Refractory disease is usually defined as non-response or progression within 90 days of treatment completion, whereas relapsed disease is considered to be early (within 3-12 months of first treatment) or late (>12 months following first treatment).

Treatment strategies for patients with relapsed and refractory Hodgkin lymphoma (RR-HL) include:

- **Autologous stem cell transplantation** (ASCT) continues to be the standard of care but most salvage and conditioning regimens have not been evaluated in randomised trials.
- For those patients not eligible for ASCT, or those with multiply relapsed HL, the introduction of novel therapeutics with promising single-agent activity may represent a paradigm shift with regards to disease control and outcome.
- In select cases, allo-SCT may continue to play a role in achieving long-term disease-free survival.
- Several salvage options are available with comparable response rates, and the choice can be dependent on comorbidities and logistics. Radiation therapy can also improve the remission rate and is an important therapeutic option for selected patients.

If salvage treatment is considered, it is recommendable to confirm the disease histology. In suspected relapsed/refractory Hodgkin Lymphoma the positive predictive value of post-treatment FDG* avidity on PET scan can be variable, and other causes should be excluded.

[*Fluorodeoxyglucose (FDG) positron emission tomography (PET) was formally incorporated into standard staging for lymphomas in 2014 (Lugano classification). FDG PET-CT has supplanted the utility of bone marrow biopsy in HL because it is capable of characterising a viable tumour (or its absence) in residual masses with diagnostic accuracy of 80 to 90%. Consequently, FDG-PET better reflects tumour response in lymphomas despite the poorer spatial resolution. It is more sensitive than CT in detecting small volume tumours, including in lymph nodes of normal size in a CT scan (i.e. < 1 cm) because of better contrast due to intense uptake by certain pathological lymph nodes relative to adjacent normal tissues.]

In the absence of a gold standard salvage regimen, the treatment decision must take into consideration the likely toxicity for the patient, the effect on stem cell mobilisation and context of delivery, such as an outpatient setting.

Salvage with single-agent BV allowed 28-35% of patients to proceed with ASCT without further chemotherapy, whereas an additional 35-40% of patients achieved PET negativity after sequential chemotherapy and were able to undergo ASCT. Increasingly, research is evaluating newer combinations incorporating agents such as bendamustine (e.g. in combination with gemcitabine and vinorelbine -BeGV regimen), brentuximab vedotin (BV) and checkpoint inhibitors.
Secondary salvage in patients who fail to achieve at least a partial remission to first line salvage regimens is possible and a number of patients may achieve good outcomes.

PROGNOSTIC FACTORS IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA

Older predictors of poor outcome:
- time to relapse after first treatment (<12 months)
- presence of advanced stage or extranodal disease at relapse
- poor performance status, have been identified as.

Modern predictors of poor outcome:
- lack of chemosensitivity pre-autologous stem cell transplantation (ASCT) salvage therapy
- residual disease at the time of ASCT.

Functional imaging after salvage chemotherapy has become increasingly useful as a predictive biomarker for response assessment: a negative (no cancer activity) PET scan after salvage treatment may be predictive of improved progression-free survival (PFS) post-ASCT, whereas positive residual PET was shown to be associated with poorer post-ASCT outcomes, even if a partial response (PR) had been achieved by conventional CT imaging.

It is important to understand the biology underlying RR-HL to offer a better approach to predicting prognosis. A novel, clinically ready test, using tissue biopsies obtained at lymphoma relapse, called RHL30, can identify the subset of relapsed HL patients at highest risk of subsequent treatment failure. This provides a foundation for informed clinical decision making, supporting the use of high dose chemotherapy and ASCT as a second-line regimen in low risk patients or suggesting alternative therapeutic approaches, such as targeted or immunotherapy, for high-risk patients.

Biomarkers, both prognostic and predictive, are urgently needed in this challenging patient group, to allow risk-adapted treatment approaches.

HIGH DOSE CHEMOTHERAPY AND ASCT

The rationale for high dose therapy and ASCT was established by two randomised trials which demonstrated a significant advantage in progression free survival (PFS) in this patient group although there was no difference in overall survival (OS). Both these studies used BEAM (carmustine, etoposide, cytarabine, melphalan) as the conditioning regimen, but other regimens have been evaluated largely in institutional series reporting comparable toxicities and outcomes.

High dose sequential strategies (HDSS) or tandem ASCT have not clearly demonstrated improved outcomes in patients with RRHL.

POST-ASCT CONSOLIDATION APPROACHES

Post-ASCT consolidation with radiation, mainly to sites of bulk, residual disease, or localised relapse may be of benefit, although there are no randomised comparisons.

ALLO-SCT

The role and timing of allo-SCT in the setting of RR-HL remains poorly defined. Early approaches using myeloablative conditioning regimens reported unacceptable rates of treatment-related mortality. Reduced intensity conditioning approaches showed the feasibility of various stem cell sources, including sibling (SIB), matched-unrelated donor (MUD) and umbilical cord blood, with PFS and OS of 20-40% and 40-60%, respectively.
A recent retrospective EBMT study found that post-transplantation cyclophosphamide-based haploidentical (HAPLO) transplantation leads to similar survival outcomes compared with SIB and MUD, and suggested that HAPLO may result in a lower risk of chronic graft-versus-host-disease (GvHD) than MUD transplantation.

**TARGETED THERAPIES**

Newer agents with novel mechanisms of action are under investigation to improve response rates for patients with subsequent relapse, though are not curative alone.

**Brentuximab Vedotin (BV)** and the checkpoint inhibitors nivolumab and pembrolizumab are very effective with limited side effects and can bridge patients to curative allogeneic transplants.

BV maintenance after ASCT is beneficial in patients at high risk of relapse, especially those with more than one risk factor, but can have the possibility of significant side effects, primarily neuropathy.

The combination treatment regimen based on brentuximab vedotin (BV) plus ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) followed by autologous stem cell transplant (ASCT) showed to be safe and effective for remission induction for patients with relapsed/refractory Hodgkin lymphoma prior to transplant. Investigators aimed to evaluate the long-term results of this combination as second-line therapy prior to ASCT. The response rate increased from 71% to 83% after transplantation, which translated into a 3-year progression-free survival of 71% and time to treatment failure of 75%. Additionally, overall survival was 91% at 2.5 years.

**Nivolumab and pembrolizumab** are monoclonal antibodies to PD-1 which have significant activity in RR-HL although follow-up remains early. The phase II study of nivolumab showed ORR of 66.3% and a CR rate of 9% in patients in relapse post-ASCT and BV. Pembrolizumab was shown to have similar efficacy in a Phase II study in patients who had failed ASCT and BV (ORR 71%, CR 22%). One clinical concern with using a PD1 blocker is that patients who have been treated with checkpoint inhibitors may be more prone to “graft versus host disease” (GvHD) following allo-SCT. These agents are now being evaluated in the salvage therapy setting raising important questions regarding post-ASCT outcomes, re-treatment, and outcomes post treatment failure.

The emergence of novel agents such as BV and immune checkpoint inhibitors has opened up great opportunities to improve the survival of patients in the relapse setting. Novel therapies also appear particularly useful for patients who have chemo-resistant disease or are not candidates for SCT.
FOLLICULAR LYMPHOMA – CURRENT PERSPECTIVES AND FUTURE DIRECTIONS

Experts discussed the barriers to improvements in follicular lymphoma treatment, and what was being done to overcome these.

It turns out that the **outlook for follicular lymphoma has really improved** thanks to establishing the standard treatment of rituximab and chemotherapy. Young patients can now expect to survive for many years. Trials are still going on to see if replacing standard chemotherapy with more targeted treatments like lenalidomide improves results further.

**There’s also the question of when patients should start therapy.** Many patients are placed on ‘watch and wait’ if they have no symptoms or signs of progression and some haematologists think that giving rituximab on its own may be an alternative for these patients.

For people with more advanced disease, there is talk of giving a combination of three therapies at once (triplet therapy), which has shown promise in other blood cancers like myeloma. Triplets tried have been combinations of targeted drugs: rituximab, ibrutinib, lenalidomide and idelalisib. Unfortunately in follicular lymphoma, the side effects like rash and stress to the liver are too severe.

**Quality of life** must be a priority to guide treatment decisions for our follicular lymphoma patients so more research is needed to offer not only quantitative survival but qualitative survival.

For the future treatment of follicular lymphoma, experts endorse the **need to find distinct treatment strategies based on the biology and risk of each individual because there are so many effective treatments now available.** With this, there is promise that doctors are moving towards targeted drugs as more become available. This is also becoming apparent for other slow growing blood cancers like chronic lymphocytic leukaemia.
OPTIMAL ENDPOINTS IN FOLLICULAR LYMPHOMA

Optimal endpoints in FL?

Patient’s perspective
- Relief of symptoms
- Information about the disease
- Cure of the cancer
- Tolerability of treatments
- Treatment-free intervals
- Fear of disease recurrence

Physician’s perspective
- Efficiency of treatment
  - CR rate
  - PFS probability
- Manage treatment-associated toxicities
- Maintenance
- Long-term follow-up
- Risk of histological transformation

TIMELINE FOR A CHEMO-FREE WORLD FOR FOLLICULAR LYMPHOMA

Timeline for a Chemo-Free World for FL


Year (approx)

- R-Mono
  - ORR 48%
  - CR 6%
- R+ Galiximab
  - ORR 72%
  - CR 48%
- R+ Epratuzumab
  - ORR 88%
  - CR 42%
- R² Relapse
  - ORR 76%
  - CR 26%
- R² Front-line
  - ORR 95-98%
  - CR 72-87%
- Idelalisib Approval
  - ORR 57%
  - CR 6%
- Copanlisib Approval
  - ORR 58%
  - CR 14%
Diffuse Large B-Cell Lymphoma (DLBCL)

The current standard of care for DLBCL patients is high dose chemotherapy followed by auto-SCT; however, only a minority of patients actually receive transplant; approximately 50% are ineligible due to age or infirmity.

Current studies suggested that the use of front-line high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) in untreated high-risk DLBCL does not improve the outcome, while this approach remains the standard of care for chemo-sensitive relapse/refractory (R/R) DLBCL. However, the outcome of many R/R DLBCL still remains unsatisfactory.

Recently, several novel agents have demonstrated promising results in R/R DLBCL patients. However the applicability of these results to real world patients in unclear as patient information from population-based cohorts in DLBCL are scarce.

Unfortunately, many hospitals and clinics omit anthracycline in older patients with DLBCL lymphoma only because of age and treat them with RCVP or BR, although older patients still benefit from the use of Rituximab and anthracycline no matter their gender or age group.
For patients receiving no treatment or palliative treatment only (12%) were older (median age 83 years) and had worse WHO performance status (84%) compared to patients treated with curative intent. 12% were refractory and 11% had relapsed.

Second line palliative therapy was offered to 45% of refractory (median overall survival 0.96 years) and to 59% of relapsed patients (median overall survival 2.9 years) and consisted of chemotherapy, radiotherapy, steroids, or supportive care.

**CONCLUSIONS**

In this detailed population-based BLBCL cohort, the primary findings were that:

- palliative patients
- patients unable to complete first-line therapy
- patients with refractory disease

were identified as subgroups with an exceptionally poor prognosis.

This substantial group of 34% of all DLBCL patients, who had a lower performance status and were older, **might benefit from less toxic (up-front) novel therapies**. In addition, given the response rates to palliative second-line therapy in relapsed patients, this group should be considered for participation in clinical trials investigating novel approaches.
NEW AGENTS BEING DEVELOPED IN B-CELL LYMPHOMA

- Naked antibodies (anti-CD20 & others)
- Antibody drug conjugates
- Bispecific antibodies
- Immune checkpoint blockers
- IMiDs
- Cell signaling (BCL & others)
- Intracellular trafficking
- Apoptosis
- Epigenetic
- CAR-T therapy
Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma and its incidence rises with increasing age. Several studies have confirmed that rituximab combined with chemotherapy is the best treatment option, but few randomised trials included patients over 80 years of age. Anthracycline-based treatment in combination with rituximab offers a potential cure but comes with substantial risk of adverse events, especially in elderly patients. The treating doctor always has to consider the individual patient’s co-morbidity and risk of complications.

The Swedish Lymphoma Registry (SLR) provided data on diagnosis, clinical factors and therapy and survival status on all patients ≥80 years diagnosed with DLBCL in Sweden 2007 through 2012.

In total 799 patients ≥80 years were identified from the SLR; 47% were male and 53% female. At diagnosis, age-adjusted international prognostic index (aaIPI) ≥ 2 was seen in 49% and bulky disease in 20%. Patients treated with anthracycline-based treatment with curative intention (R-CHOP-21, R-CHOP-14, R-CHOEP) showed significantly better survival with a hazard ratio (HR) of 2.5 (95% confidence interval [CI], 2.2-3.0) compared with patients treated with palliative regimens or no chemotherapy at all. In the Regional analysis, two Regions treated a relatively large proportion of their elderly patients with curative intent (58% in total) whereas three Regions showed a lower fraction (43% in total) and one Region deviated with a considerably low percentage (33%). These treatment differences were highly significant (p<0.001). The overall survival was also significantly better in the more intensive Regions compared with the less intensive and the least intensive Region, HR 1.3 (95% CI 1.1-1.6) and HR 1.5 (95% CI 1.2-1.9).

This large, nationwide, population-based study shows that anthracycline-based treatment with curative intention is associated with improved survival also in the very elderly patients over 80 years of age. Furthermore, we can show that the proportion of patients treated with curative intention vary between different healthcare Regions in Sweden suggesting different routines when it comes to treating the very elderly. Regional differences were used to validate results by showing that Regions with more intensive treatment traditions have better overall survival. This analysis can be seen as a geographic randomisation that is unaffected by response to therapy and co-morbidity since the intensity of treatment is significantly differs merely on the basis of region. The researchers concluded that patients over the age of 80 years benefit from anthracycline-based treatment with curative intention.
CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

TOWARDS CONTROL OF CLL USING ‘CHEMOTHERAPY-FREE’ COMBINATIONS

The last two decades have witnessed an unprecedented progress in the management of chronic lymphocytic leukaemia:

- use of whole exome sequencing,
- clinical CLL databases that allow better descriptions of the genomic landscape in CLL
- stimulation of the B-cell receptor
- interaction of CLL cells with their microenvironment
- better understanding of conventional therapies with alkylators and monoclonal antibodies or with kinase inhibitors (KI)

Inspired by this progress, new therapeutic options have become available. As a consequence, the management of patients with CLL is currently undergoing profound changes and the outcome of first-line therapies has markedly improved. The choice of initial therapy (e.g. by adding CD20 antibodies to chemotherapy) creates a survival benefit for CLL patients.

More recently, the advent of targeted agents such as ibrutinib, idelalisib and venetoclax, has increased our therapeutic armament even further. Finally, CAR-T cells are also effective therapies for some CLL patients but their definitive place remains to be determined. The comparison of the overall response rates and minimal residual disease (MRD) negative remissions obtained with various treatment options illustrates this quite impressive progress (Figure 1).

The so-called “real-world” observations suggest that ibrutinib appears superior to idelalisib when used as first kinase inhibitors (KI). In the setting of kinase inhibitors failure, alternate KI or venetoclax therapy appear superior to chemo-immunotherapy.

Together, these data lend further support for clinical studies that optimise the sequencing strategy to treat patients (one therapy first, then the other).

The focus now is moving to establishing how to achieve long-lasting remissions, eradicate residual disease or even offer cure for CLL patients.

New research tries to understand the benefit behind the use of sequential or combination therapy, and the assessment of prognostic factors to guide the treatment selection.
New combination therapies appear very promising, in particular when combining anti-CD20 antibodies with targeted agents. For example, the “CLL2-BAG protocol” (using bendamustine, venetoclax and obinutuzumab) yielded excellent overall response and minimal residual disease (MRD) negative response rates of around 90% both in treatment naïve and pre-treated patients. Similarly, the “Murano trial” yielded MRD-negative response rates of 83.5% using venetoclax plus rituximab in relapsed CLL patients. Finally, kinase inhibitors may enhance the function of T-cells. It was shown that >/=5 cycles of ibrutinib therapy improved the expansion of CD19-directed CAR T-cells (CTL019), in association with a decreased expression of the immunosuppressive molecule programmed cell death 1 on T-cells and of CD20 on B-CLL cells.

Taken together, it is obvious there is the potential for a long-term control of CLL.

HALF OF CLL PATIENTS WHO RELAPSE ON BRUTONS TYROSINE KINASE (BTK) INHIBITORS HARBOUR BTK/PLCG MUTATIONS

A relationship between the mutation in Brutons tyrosine kinase (BTK) and associated PLCG2 genes and the risk of relapse has been established for patients with CLL who have received Brutons tyrosine kinase inhibitor in the course of their CLL treatment.

Dr Lydia Scarfo (San Raffaele Scientific Institute, Milan, Italy) explained how (in the context of a multicentre international study) 50% of CLL patients who have received Brutons tyrosine kinase inhibitor ibrutinib in the course of their CLL treatment and relapsed harbour mutations in BTK and associated PLCG2 genes.

The relevance of this co-relationship, could lead to new approaches for screening and personalized treatment guidance.
However, while BTK/PLCG2 mutations have characteristics suggesting that they can drive ibrutinib resistance, this conclusion remains formally unproven until specific inhibition of such mutations is shown to cause regression of ibrutinib-resistant CLL. Data suggest that alternative mechanisms of resistance do exist in some patients.

Time will define how to properly address these findings for guiding treatment decisions that could benefit patients.

**Concluding Summary**

- We analyzed 22 relapsed and 32 responding CLL patients treated with ibrutinib
- Around 50% of cases relapsing on ibrutinib had $BTK^{C481S/R}$ mutations
- $PLCG2$ mutations were rare overall: 3 relapsed cases with $PLCG2$ mutations all carried $BTK^{C481S/R}$ mutations
- These results indicate the outgrowth of several resistant clones during ibrutinib treatment
- It remains to be established the mechanisms leading to resistance in cases without $BTK/PLCG2$ mutations

Half of Chronic Lymphocytic Leukaemia patients relapsing under ibrutinib carry BTK and PLCG2 mutations. A European Research Initiative on CLL (ERIC) Real World study. Dr. Scarfo L. Jun 17, 23 EHA congress 2018.
QUALITY OF LIFE IN CUTANEOUS T-CELL LYMPHOMA SUBJECTS TREATED WITH ANTI-CCR4 MONOCLONAL ANTIBODY MOGAMULIZUMAB VERSUS VORINOSTAT: RESULTS FROM THE PHASE 3 MAVORIC TRIAL

Conclusions

- MAVORIC is the largest Phase 3 trial of systemic treatment in CTCL to date (N=372). Patient reported outcomes, measured by Skindex-29 and FACT-G, demonstrated a significant QoL benefit in MF/SS patients given mogamulizumab compared to vorinostat.
- A significant benefit for mogamulizumab on symptom, emotional, and functional scales were seen as early as cycle 3 for all domains of Skindex-29 and FACT-G.
- Mogamulizumab resulted in clinically meaningful improvements in patient-reported symptoms and preservation of physical well-being.
- 61% of patients randomized to mogamulizumab reported clinically meaningful improvements in symptoms beginning at cycle 3 and lasting throughout treatment.
- Mogamulizumab delayed deterioration from baseline in both symptoms and functional status in this study, where patients were treated until progression or intolerance (a time when decreased QoL is expected). The delay in patient-reported worsening in skin symptoms was most pronounced in SS.
Anaemia and fatigue are frequent indications for WM treatment. To date, patient-reported outcomes (PROs) have not been used to quantify benefits of any WM treatment.

- Ibrutinib, a first-in-class, once-daily inhibitor of BTK, is indicated in the EU for the treatment of WM after ≥1 prior therapy or first-line in patients (pts) unsuitable for chemo-immunotherapy.
- PRO assessments—FACT-An total score (TS) and FACT-An anemia subscale (AS), and EQ-5D-5L (EQ)—were performed regularly.
- Persistent fatigue was the main indication for treatment in 22/31 (71%) patients.

Baseline Patient Reported Outcomes scores were lower for the sub study vs randomised patients. With a median of 17 months of treatment, most patients had clinically meaningful improvement in FACT-An Score (TS ≥7 points; 77%), FACT-An Anemia Subscale (AS ≥6 points; 84%), and EQ-5D-5L (EQ utility scores ≥0.08 points; 68%).
Time to clinically meaningful improvement was prompt (1 month for TS and AS; 2 mo for EQ), corresponding with a 48% decline in median IgM (median 20 g/L) after 4 weeks. In patients with baseline anaemia (haemoglobin [Hb] ≤110 g/L), sustained Hb improvement increased with depth of response.

At week 65, Hb levels significantly correlated with TS (r=0.507, P=0.01) and AS (r=0.519, P=0.008), and were marginal for EQ (r=0.39, P=0.054). Although IgM levels did not significantly correlate with PRO scores, the benefit was similar in responders regardless of depth of response.

**IMMUNOTHERAPY**

The complex relationship between the immune system and cancer development has been the subject of investigation for decades. Improved understanding of the interactions between cancer cells and the immune system combined with technological advances has led to the development of novel types of immunotherapies, which have demonstrated remarkable efficacy for the treatment of cancer. In lymphomas three of these new immunotherapies appear to be particularly promising:

- **Immune Checkpoint Inhibitors**
  - cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)
  - programmed death-1 (PD-1)
- **Chimeric Antigen Receptor (CAR) T-cells**
- **Lymphoma Neoantigens**

Each of these approaches has its own advantages and disadvantages and benefit different patients.

Some of these immunotherapies have already been granted approval by the FDA or EMA for haematological malignancies (anti-PD1 antibodies in Hodgkin lymphoma, and CAR T cells in diffuse large B-cell lymphoma).

In the future, these approvals are likely to be extended to other lymphoma subtypes. The new immunotherapies should be seen as complementary rather than competitive.

This is the beginning of a new and exciting era in which each patient will be offered a “personalised immunotherapy” based on the status of his tumour and immune system.

**CAR-T THERAPY IN DIFFUSE LARGE B-CELL LYMPHOMA**

One of blood cancer’s hottest topics at the moment has been reflected in EHA’s theme this year: immunotherapy, frontiers in haematology. CAR-T therapy has been big on the agenda, and there was lots of discussion around this new development.

Around 80% of people with diffuse large B cell lymphoma (DLBCL) respond well to standard first line treatment. This is made up of rituximab (a type of immunotherapy that targets CD20 on the surface of lymphoma cells) and chemotherapy. But when people relapse after this treatment, it gets harder and harder, and chances of survival are radically cut as different treatments are tried and fail. This is where CAR-T therapy makes an appearance.
**CAR-T therapy is the new immunotherapy**, where a patient’s T cells (a type of immune system cell) are changed in the laboratory so they will attack cancer cells. In some DLBCL patients who were not responding to existing treatment, **CAR-T therapy has had remarkable effect and has taken patients who only had months to live into remission**.

But there are **still issues that we need to address with CAR-T therapy**. For example safety, which is a concern, because patients are at risk of suffering side effects such as ‘cytokine storms’ and neurological toxicity (confusion, loss of memory etc.) happening within the first 30 days.

**Cytokine storms** are where CAR-T cells unleash massive amounts of proteins called cytokines, which stimulate other elements of the immune system to attack the cancer cells. This can cause flu like symptoms, such as high fevers and extreme fatigue, but also difficulty breathing, and a sharp drop in blood pressure (which can in some cases be life-threatening). Cytokine storms luckily can often be dealt with by giving the patient an antibody to counteract the affects, and steroids can be given to stop the neurological issues. Doctors are also beginning to understand which patients are more likely to get these effects, and are starting to think of ways to deal with this.

Other issues discussed in the congress were **costs associated to CART-T therapy, logistics of providing the therapy and challenges to administering CAR-T**. There is a general view that the price will come down once the competition increases among the pharmaceutical companies. **As CAR-T is rolled out into different healthcare systems, upscaling and future innovations are sure to happen**.

With all this to take in, there has also been talk on where CAR-T therapy may sit in the future treatment line for DLBCL. Should we be thinking about treating people that we know are high risk of relapsing (based on the genetic and biological make-up of their lymphoma)? Only time will tell.

**ACCESSIBILITY TO CAR-T THERAPY FOR AGGRESSIVE B-CELL LYMPHOMAS**

CD19 targeting CAR T-cell therapy for R/R aggressive B-cell lymphomas is different from conventional therapies in many aspects. Costs of both the cell-product and the treatment and management of adverse events cannot be exactly assessed yet; however, the list price of CAR-T therapy could cost about half a million euros per patient. Additional costs will arise from adverse event management. About a third of all patients will need intensive care monitoring including tocilizumab, vasopressors, and oxygen supply. Although reliable numbers of additional costs for individual patients are not available yet, prices by far exceed any other approved treatment for B-cell lymphoma and may cause specific regulatory issues. In addition, the industry still has to implement sufficient production capacities, if all patients with R/R aggressive B-cell lymphoma were treated with this approach.

Finally, specialist treatment centres and CAR T-cell teams still need to be properly trained and qualified to administer the treatment. For the time being, treatment capacities of qualified centres might not be sufficient to meet the needs. Overall, there are many difficulties to overcome before CAR T-cell therapy for malignant lymphoma can be called “established” and it will take major efforts from the national authorities, the respective healthcare systems, and the physicians to make it widely available to patients.
CAR T-cell therapy is still only a promising therapy and more evidence is needed to demonstrate its long-term efficacy. In summary:

- Longer follow-up of the published phase II data is necessary for definitive conclusions to be drawn. Implementation into daily routine must be established.
- Trials are already ongoing to investigate the efficacy of constructs for additional CD19 expressing lymphoma subtypes like mantle-cell lymphoma or follicular lymphoma.
- Competition in the field may hopefully result in lower prices, which may make this treatment option easier and more acceptable for society.

An alternative option might be the individual on-site production of CAR T-cells by academic institutions, which would allow production without the need for profit as it has been the case for stem-cell transplantation for many decades now.

Accessibility to CAR-T therapy for lymphoma patients

1. Isn’t it too expensive for our health-care system?
2. Will the companies be able to provide the production capacities to treat all patients suited for CAR T-cell therapy?
3. Will “everybody” be allowed to administer CAR T-cells? Risk evaluation and mitigation system (REMS)

Efficacy, safety and accessibility to CAR-T therapy for lymphomas by Peter Borchmann
The EHA congress addressed the issue of quality of life (QOL) of patients and patient reported outcomes. Several sessions included discussions on how to improve QOL assessment and how to assure that patient experience and perspective guide the reporting of adverse effects from a multidimensional point of view.

The findings from a new Commission published in The Lancet Haematology were presented during the congress. The report, which brings together 40 leading clinicians, clinical investigators, regulators, biostatisticians and patient advocates, recognises how current methods of reporting adverse events, focused on assessing a drug or regimen’s safety, often fail to also appropriately identify important delayed, chronic or cumulative effects that can affect patients substantially. Moreover, it identifies important areas for improvement of safety reporting and analysis of trials in haematological malignancies and suggested a number of potential solutions.

The authors, led by Dr. Gita Thanarajasingam, Mayo Clinic, Rochester (MN), USA who was presenting the report at the 23th EHA congress, propose new approaches to evaluating and reporting adverse events to complement the current methods. These include expanding reporting beyond high grade, acute toxic side-effects, and capturing less severe but chronic side effects, and cumulative and late effects in a more standardised manner. While short-term side effects with some regimens might include nausea and vomiting occurring over a few days in a cycle, long-term effects might include neuropathy which worsens over time with ongoing drug exposure and can persist even after therapy is complete, for example. Additionally, the authors emphasise that changes to clinical trial design to accommodate delayed adverse events, and incorporating patient reported outcomes into trials to assess and improve tolerability, adherence and quality of life, are essential.

The Commission also examines streamlined approaches to identify unexpected side effects from stem cell transplantation and improved evaluation of late- and long-term side effects in survivors.

As newer treatments in haematological malignancies are offered more widely, capturing data from population studies will be essential to understand side effects outside of clinical trial settings and in the real world. Additionally, post-marketing surveillance by regulatory agencies should adapt to include relevant data on long-term adverse events in a real world patient population.
Real world evidence: how can patients contribute?

- Co-design of:
  - Prognostic tools
  - Disease-specific PROMs for trials & clinical practice
  - PROMs for health care reform
  - Narrative medicine – Back to Life
- Access to:
  - Patient registries
  - Medical records
  - Gray literature - example
  - Safety data
  - Lobby/mobilize stakeholders

Health-Related Quality of Life (HRQoL)

- Multi-dimensional concept that captures:
  - Physical, mental, emotional, societal domains
  - Impact of health status on quality of life
- Measures (should) include:
  - Measurable outcome measures
  - Real-life outcomes measures
  - Patient Reported Outcomes Measures (PROMs)
  - Experimental data

Conclusions

- Sexual dysfunction is not a niche phenomenon, but just a major issue, heavily affecting large proportions of cancer patients.
- Just a minority of patients talk about this with their doctor, despite the potential benefits of doing so.
- Some doctors address the topic, while potential interventions may have a large effect on QoL of cancer patients during and after cancer.
- Address the topic with your patients, and if you can’t, refer them to a specialist if necessary.

Can we optimise databases for real world AE evaluation?

- PROs are not a standard part of toxicity assessment and therefore toxicity from the patient’s perspective is not assessed.
- Cumberbough reporting of the myriad of expected adverse events in the HCT setting is a barrier to performing clinical trials.
- Toxicities affecting patients in routine clinical practice are difficult to capture and analyze on a large scale.
- Measuring adverse events are often underreported to regulatory agencies, while reporting of uninformative AEs might elicit true safety signals.

Selected update on lymphoma from 23EHA congress, June 2018
“Systematic integration of PROs in clinical practice is crucial for improving patientcare” - Ton Hagenbeek just kicked off the EHA SWG ‘Quality of Life and symptoms’ session.

#EHA23

Yes! We already started at #EHA23 @EHA_Hematology / work package teams are discussing research bigdata outcomes

Dr Harpreet Kaur (Sheffield) at the Patient Advocacy Session on QoL: we need to see the patient as a person who happens to have some health problems #EHA23

patientadvocacy

Quality of Life

- Seeing the patient as a person
- Enable and empower patients, involve them in decision making and discussion
- Education should start early
- QoL a fitting routine clinical practice and simplify the process of self-reporting
- The clinician is not usually the most important person in the team