23rd Congress of EHA

European Hematology Association

14-17 JUNE 2018 • STOCKHOLM • SWEDEN

PEER-REVIEWED CONFERENCE REPORT

CLL1-CD33 CAR T-cells in Refractory AML

Researchers have recently tested their CLL1-CD33 compound CAR T-cells for the first time in a patient with refractory acute myeloid leukaemia. The results were shown at the EHA Presidential Symposium.

read more on PAGE 3

Early PET Driven Treatment Hodgkin's Lymphoma

The final analysis of the AHL2011 study demonstrated that de-escalation with a switch from BEACOPP to ABVD is possible in most patients who reach a negative PET after 2 cycles of BEACOPP.

read more on PAGE 8

Ravulizumab Only Once Every 8 Weeks in PNH

In patients with paroxysmal nocturnal haemoglobinuria, ravulizumab once every 8 weeks has shown non-inferiority to eculizumab once every 2 weeks. Both drugs are C5 inhibitors, but ravulizumab has a longer half-life than eculizumab.

read more on PAGE 13

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Editor Prof. Gert J. Ossenkoppele, VU University Medical Center, the Netherlands

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Letter from the Editor

Prof. Gert J. Ossenkoppele

Dear Reader,

At the annual meeting of the European Hematology Association held on 14-17 June 2018 in Stockholm, Sweden, nearly 12,000 participants from all over the world were informed on new developments in different areas of interest.

Basic scientists, translational haematologists, clinicians, patients, pharmacists, employees of pharmaceutical companies, and others interested in haematology attended this exciting meeting. In this report, we made a selection of interesting presentations out of the numerous talks that were given on myeloid and lymphoid malignancies, multiple myeloma, stem cell transplantation, benign haematology topics, and paediatric haematology. Many new treatment options and strategies are emerging, creating a lot of possibilities for haematology patients. Targeted treatments and immunotherapy are now rapidly evolving and are already available or will soon become available. We hope that this report will give you some insight into the recent developments in the field of haematology.

Best Regards,
Prof. Gert J. Ossenkoppele

Biography

Professor Gert Ossenkoppele was appointed in 2003 as professor of Haematology at the VU University Medical Center in Amsterdam. Gert Ossenkoppele has authored over 390 publications in peer-reviewed journals and is an invited speaker at many international scientific meetings. His research interests are mainly translational and include the (stem cell) biology of AML, leukaemic stem cell target discovery, immunotherapy, and measurable residual disease (MRD) detection using flow cytometry to inform treatment of AML. He is the PI of various clinical trials in myeloid malignancies. He chairs the AML working party of HOVON (Dutch-Belgian Haematology Trial Group) and is appointed as vice-chair of the HOVON Executive Board. He is a lead participant of the AML Work package of the European LeukemiaNet (ELN) as well as a board member of the ELN foundation. He is recently appointed as chair of the EHA Educational Committee. He chairs the AML Scientific working group of EHA, and he is chair of the Global and EU steering committee of the AMLGlobalPortal an educational portal for haematologists (www.amlglobalportal.com).

Prof. Ossenkoppele is consultant for Novartis and BMS.

photo by EHA.

We have to keep drugs affordable and accessible for everyone

Interview with EHA president
Prof. Pieter Sonneveld

conducted on 28 June 2018 by Mirjam Bedaf

This year, almost 12,000 people attended the EHA meeting. That is more than a 1,000 more participants than in 2017. Besides participants from Europe, EHA is increasingly attended by people from Asia, South-America, and the United States. Exclusively for Medicom's Conference Report, EHA president Prof. Pieter Sonneveld (Erasmus Medical Centre, the Netherlands) reflects on this year's meeting and on the challenges in the field of haematology.

Can you explain this year's EHA Congress theme?

"This year's theme is sustainability, which also fits nicely with the country where the EHA meeting was hosted this year. Sweden is all about no waste and durability. EHA is heavily involved in education, research and clinical care and firmly committed to making good clinical care available to as many patients and haematologists as possible. Unfortunately, access to new effective therapies is not distributed fairly; not even in Europe. There are countries where patients can use almost all new drugs, but there are also countries where the opposite is true. With this theme, EHA is letting go of the one-year themes because sustainability is not vital just this year. It is in fact decisive for clinical care and research year after year."

Are there specific topics that EHA wants to put in the spotlight?

"By launching the topics-in-focus programme, we want to give special attention to two topics this year: immunotherapy and haemoglobinopathies. In recent years, there has been a shift from chemotherapy to more personalised therapies, like immunotherapy, with fewer side effects. We expect a lot from this in the future. Hemoglobinopathies, on the other hand, can be invalidating at a young age and there is an unmet need for new treatments. For sickle cell disease, for example, and also for thalassemia, a disease that in Europe mainly occurs among immigrants."

As a haematologist, what do you consider promising developments at this moment?

"More and more research into the causes of haematological malignancies is being done. Cancer does not arise overnight. Early on, abnormalities in the DNA which may play a key role in the development of the disease can already be encountered. A good example of research on this topic is a large programme in Iceland. The limited number of inhabitants share many genetic similarities. Investigators from the University of Iceland are searching for mutations that can lead to haematological diseases. Furthermore, I expect a lot from the Harmony programme, a large programme by the European Commission in which universities, hospitals, pharmaceutical companies, and authorities work together to collect the enormous amount of data about haematological malignancies that is available in Europe. With this big data set we can investigate why certain groups of patients respond more easily to a certain therapy than others, for example. Or to examine why we see late effects after radiation in some people but not in everyone?"

Are there any other challenges?

"Apart from medical developments, keeping the prices of medicine manageable remains a big challenge. We have to keep drugs affordable and accessible for everyone and not just for one small group. We realise that our influence does not extend globally, but by organising it properly in Europe I am convinced that this will also be tackled elsewhere in the world. Our colleagues from the American Society of Hematology in the United States are also keen on this topic and we try to work together on this."

The combination of your work as a haematologist and professor with the EHA presidency is probably also challenging. How do you combine the two?

"The president of EHA is always an active haematologist, someone who is a professor as well as a Head of Department. Of course, the role of EHA president is time consuming and you have to be organised. But, luckily, EHA is an efficient organisation. The EHA office does an excellent job and takes care of a lot of practicalities. We work with an executive board that includes the president, the former president, and the president-elect. After two years of presidency I will resign, but I will remain closely involved. In this way, we transfer our knowledge and ensure continuity."

Myeloid Malignancies

With the rise of new drugs and new treatment options, the prognosis of patients with myeloid malignancies has improved in recent years. At this year's EHA meeting, hopeful results of a new CAR T-cell therapy were presented: the first human study on CLL1-CD33 CAR T-cells in refractory acute myeloid leukaemia (AML). Also presented at EHA 2018 were the final data from the DESTINY study and the QuANTUM-R trial. And finally, investigators strongly recommend the ELTS score instead of the Sokal score for the prediction of long-term survival in patients with chronic phase chronic myeloid leukaemia (CP CML).

Quizartinib in patients with R/R FLT3-ITD–mutated acute myeloid leukaemia

The first report of the global phase 3 QuANTUM-R trial, presented as late-breaking abstract, showed that the single-agent quizartinib significantly prolonged overall survival (OS) in patients with relapsed/refractory (R/R) FLT3 internal tandem duplication (*FLT3*-ITD)-mutated acute myeloid leukaemia (AML) compared with salvage chemotherapy [1]. These pivotal data confirm the efficacy and safety of quizartinib and the value of targeting the *FLT3*-ITD driver mutation with a highly potent and selective FLT3i, stated Dr Jorge Cortes.

FLT3-ITD is a common driver mutation in AML and is associated with high leukaemic burden and poor prognosis. Patients have high risk of relapse, decreased response to salvage therapy, and a shorter OS. Currently, there are no approved targeted therapies for those patients, which represents a high unmet medical need. Quizartinib is a once-daily, oral, highly potent, and selective FLT3 inhibitor, which has shown in phase 2 trials to have promising single-agent antileukaemic activity with a manageable safety profile.

In total, 367 patients were randomised to quizartinib (n=245) or salvage chemotherapy (n=122 [LoDAC n=29; MEC n=40; FLAG-IDA n=53]). Of the patients treated with quizartinib, 80 (32.7%) patients were refractory to and 165 (67.3%) relapsed after a CR1 of <6 months. Similarly, 41 (33.6%) patients treated with salvage chemotherapy were refractory to and 81 (66.4%) relapsed after a CR1 <6 months. The OS HR of quizartinib relative to salvage chemotherapy was 0.76 (95% CI 0.58-0.98; P=0.0177). Median OS was 27 weeks (95% CI 23.1-31.3) and 20.4 weeks (95% CI 17.3-23.7) for patients treated with quizartinib and salvage chemotherapy, respectively. Estimated survival probability at 52 weeks was 27% for the quizartinib arm and 20% for the salvage chemotherapy arm. Toxicity was comparable between the treatment arms.

First human study on CLL1-CD33 CAR T-cells in refractory acute myeloid leukaemia

Chinese investigators have recently tested their CLL1-CD33 compound chimeric antigen receptor (CAR) T-cells for the first time in a patient with refractory AML [2]. The results of the phase 1 study were shown at the EHA Presidential Symposium. Anti-CD19 CAR T-cells have previously shown impressive results in patients with B-acute lymphocytic leukaemia (B-ALL) and lymphoma, and have now been approved by the FDA. However, the treatment of recurrent and refractory AML with CAR T-cell therapy remains a challenge, since AML consists of heterogeneous cells. Therefore, the investigators developed CAR T-cells directed against CLL1 and CD33. CLL1 is specifically expressed on leukaemic stem cells (LSC) in contrast to normal stem cells. LSC play a substantial role in disease progression or relapse. CD33 is a myeloid marker found in most patients with AML.

In vitro assays showed that the CLL1-CD33 CAR T-cells have specific anti-tumour activity in cell lines expressing CLL1 or CD33, as well as in samples from AML patients. In mouse models, CAR T-cells reduced tumour burden and prolonged survival. Anti-CD52, alemtuzumab, appeared to be useful in mouse models as a safety switch, in order to terminate the treatment quickly if necessary. In the phase 1 study, treatment with the CLL1-CD33 CAR T-cells was well tolerated. So far, one patient was treated who achieved a complete response.

Final results DESTINY study

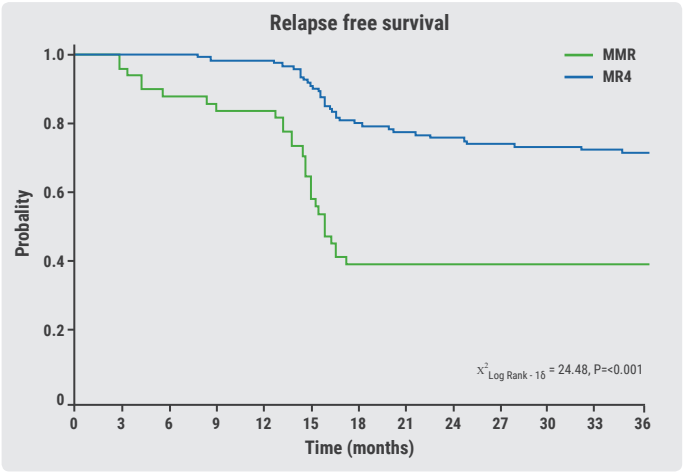
In the second stopping year of the DESTINY study of de-escalation and stopping treatment in chronic myeloid leukaemia (CML), minimal (only 5) recurrences occurred [3]. The British study of De-Escalation and Stopping Treatment with Imatinib, Nilotinib, or sprYcel (DESTINY) recruited 174 patients from December 2013 until April 2015. Entrants were

in first chronic phase, on the same tyrosine kinase inhibitor (TKI) for at least 3 years since original diagnosis (although 1 change was permitted if intolerant to the initial TKI), and with all *BCR-ABL* qPCR transcript levels (minimum of 3) <0.1% in the 12 months before entry. If all these results were also <0.01%, they were assigned to the MR4 group; patients with one or more result between 0.1% and 0.01% were allocated to an MMR but not MR4 group. Thus, entry criteria were almost identical to the EUROSKI study except that patients with MMR but not MR4 were also separately eligible.

TKI treatment was de-escalated to 50% of the standard dose (imatinib 200 mg daily, dasatinib 50 mg daily, or nilotinib 200 mg twice daily) for 12 months, then stopped altogether for a further 24 months. At entry, 148 patients were receiving imatinib, 16 nilotinib, and 10 dasatinib, for a median duration of 6.8 years. Previously, the investigators reported that after 24 months of study, molecular recurrence was lower in patients with stable MR4 at entry (29 of 125 patients; 23.2%) than in those in MMR but not MR4 (29 of 49 patients; 59.2%; P<0.001). Now the long-term results are also available: in the 12 months of complete treatment cessation, only 5 further recurrences have occurred. They all occurred in patients with stable MR4 at entry, giving a recurrence-free survival (RFS) of 72% (90% CI 65-79) at 36 months follow-up in this group of patients (Figure 1). The overall recurrence rate is higher in the MMR but not MR4 group (20 of 36 patients during cessation; 39% RFS overall [90% CI 29-52]; P<0.001).

According to the British investigators, these findings suggest that initial de-escalation is not simply delaying recurrence, though the mechanism of its benefit is not yet clear. Possibilities include gradual mobilisation of leukaemic stem cells into cycle and/or gradual improvement in the anti-leukaemic immune response at a time when TKI is still present. These require further study, they explained.

Figure 1 Final results DESTINY study: relapse free survival after de-escalation and stopping treatment in chronic myeloid leukaemia (CML) [3]



ELTS score recommended over Sokal score with chronic phase CML

The European Treatment and Outcome Study (EUTOS) long-term survival (ELTS) score is superior to the Sokal score for prognosis of survival probabilities of patients with chronic phase chronic myeloid leukaemia (CP CML) [4]. Therefore, the EUTOS investigators recommend the use of the ELTS score for prediction of long-term survival. Still, many investigators continue to apply the Sokal score for the prognostic discrimination of CML patients treated with TKIs.

The ELTS score was initially developed in 2,205 imatinib-treated patients from the EUTOS registry, which contains data on adult patients with CP CML, in order to discriminate 3 risk groups with different probabilities of dying from CML. The Sokal score had allocated 23% of patients to the high-risk group; the ELTS score 12%. Because long-term outcome of TKIs suggests that allocating >20% CP CML patients into a high-risk group is too pessimistic, the authors did an analysis to compare risk group allocations and prognosis between the 2 scoring systems. Due to the success of TKIs, the number of deaths from CML has distinctly declined. Therefore, 2,949 patients from other registry sections were added, making a total of 5,154 patients.

Six-year OS probability was 90%. Of 429 deceased patients, in 175 CML progression prior to death was confirmed (40%). The 6-year cumulative incidence probabilities (CIPs) of dying of CML was 4%. From low to high risk groups, the Sokal score resulted in 6-year CIPs of 3%, 4%, and 8%, while the ELTS score resulted in 6-year CIPs of 2%, 5%, and 12%. Of the 1,197 patients allocated to high risk by the Sokal score, the ELTS score classified 671 (56%) as non-high risk. The Sokal high-risk patients but ELTS non-high-risk patients (6-year OS 88%) showed higher OS than the 526 common high-risk patients (6-year OS 81%). As these patients had significantly and clinically relevant lower CIPs of death and higher OS probabilities, the allocation of the Sokal score was not appropriate.

References

1. Cortes J, et al. EHA 2018, LB2600.
2. Liu F, et al. EHA 2018, abstract S149.
3. Clark R, et al. EHA 2018, S809.
4. Pfirrmann M, et al. EHA 2018, S811.

Lymphoid Malignancies

Aiming to improve prognoses, several new combinations of treatment options are being tested; especially in patients with relapsed or refractory disease. This chapter covers the results of the RELEVANCE trial, CLL11 study, iNNOVATE trial, and real-world data about CLL, HL, and DLBCL.

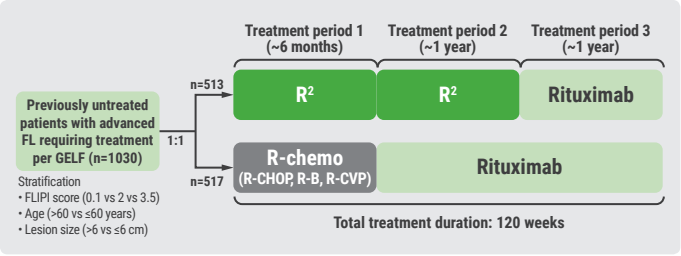
Effect of BTK and PLCG2 mutations on relapse in ibrutinib-treated chronic lymphocytic leukaemia

Preliminary results of a real-world, multicentre, international study from the *European Research Initiative on chronic lymphocytic leukaemia* (CLL; ERIC) revealed that 50% of cases relapsing on ibrutinib had Bruton's tyrosine kinase (BTK) gene at C481 mutations that are often associated with *PLCG2* mutations [1]. The findings were presented at EHA 2018 in a late-breaking abstract. Acquired mutations at BTK^{C481}, the binding site for ibrutinib, or, more rarely, in the PLCG2 gene, have been reported in pre-relapse and post-relapse samples of ibrutinib-treated CLL patients. Till now, real-world evidence was lacking regarding the frequency of such mutations in relapsing patients but also those with sustained responses. The investigators analysed samples of 79 CLL patients treated with ibrutinib (28 relapsed and 51 still responding at last follow up >1 year from therapy initiation). The absence of mutations in these genes was associated with a longer time to progression. These results indicate the outgrowth of several resistant clones and suggest multiple resistance mechanisms that need to be studied towards eventually designing innovative treatment to improve the outcome of CLL patients relapsing on ibrutinib.

Lenalidomide plus rituximab in follicular lymphoma

The addition of lenalidomide to chemo-immunotherapy in patients with previously untreated follicular lymphoma (FL) has similar results in response but has a better safety profile than the standard chemo-immunotherapy, concluded the RELEVANCE investigators [2]. Chemo-immunotherapy followed by rituximab maintenance is the standard treatment for patients with previously untreated, symptomatic FL. In these patients, a combination with lenalidomide and rituximab (R2) has shown promising first results. Moreover, the results of the phase 3 RELEVANCE study on R2 vs standard chemo-immunotherapy have been presented.

Figure 2 RELEVANCE study design [2]



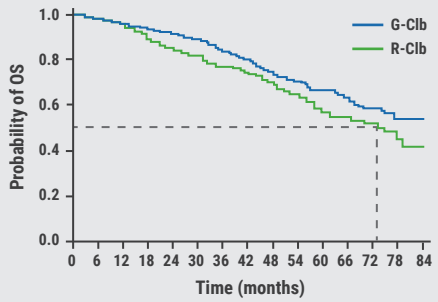
In the RELEVANCE study, 1,030 previously untreated FL patients were randomised 1:1 to a 120-week treatment with standard treatment or R2 (Figure 2). After a median follow-up of 37.9 months, complete remission was comparable in both groups: R2 48% vs R-chemo 53%, and the 3-year PFS was 77% and 78%, respectively. The OS after 3 years was high for both arms: 94%. However, the safety profile was different. With R-chemotherapy, grade 3/4 neutropenia (R2 34% vs R-chemo 50%) and febrile neutropenia (R2 2% vs R-chemo 6%) occurred more frequently; with R2 more grade 3/4 cutaneous reactions occurred (R2 7% vs R-chemo 1%). Second primary malignancies were reported in 7% of patients in the R2 arm and 9% of patients in the R-chemo arm. This makes lenalidomide plus rituximab a potential new first-line option for patients with FL, according to the authors. Patients are still being followed in order to obtain more mature PFS and OS results.

CLL11 study: final results obinutuzumab vs rituximab

The final results of the international CLL11 study confirm the combination of obinutuzumab plus chlorambucil as first-line treatment for patients with CLL and comorbidity [3]. In the CLL11 study, 781 untreated CLL patients with comorbidity were randomised 1:2:2 to 6 28-day cycles with chlorambucil (Clb), rituximab plus Clb (R-Clb), or obinutuzumab plus Clb (G-Clb).

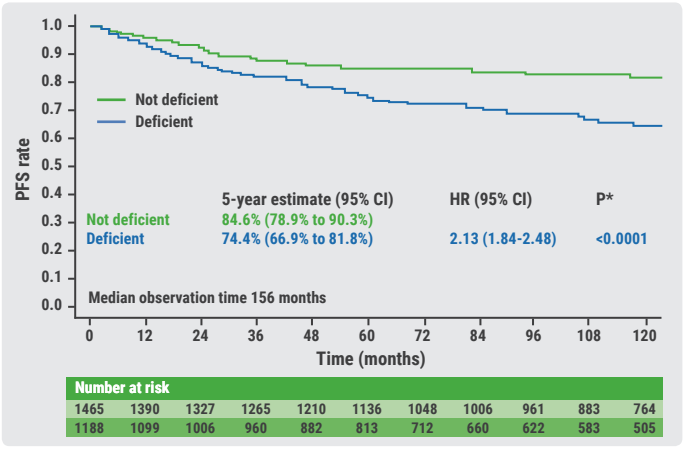
Obinutuzumab is a glycoengineered, type II, anti-CD20 monoclonal antibody that is able to attack CLL by binding

Figure 3 Final results CLL11 study: obinutuzumab vs rituximab [3]



	G-Clb n=333	R-Clb n=330
Median OS, months	NR	73.1
HR (95% CI), P-value	0.76 (0.60-0.97), P=0.00245	

Figure 4 Vitamin D deficiency and PFS in Hodgkin's lymphoma [4]



Number at risk										
1465	1390	1327	1265	1210	1136	1048	1006	961	883	764
1188	1099	1006	960	882	813	712	660	622	583	505

* P-value obtained from weighted Cox regression stratified by study/treatment arm and adjusted for diagnosis season, age and sex

and destroying malignant CLL cells. Rituximab is a non-glycoengineered, type I, anti-CD20 monoclonal antibody that also binds and kills CLL cells. Previous analyses of the study, with median observation times of approximately 20 and 40 months, demonstrated a longer PFS in both the R-Clb and the G-Clb arm, and a longer OS in the G-Clb arm. The results of the final analysis, presented at EHA 2018, showed G-Clb not only to be superior to R-Clb with respect to PFS, but also with regard to overall survival.

After a median follow-up of 62 months, treatment with G-Clb (n=238) was superior to treatment with Clb alone (n=118): PFS was 31.1 vs 11.1 months (HR 0.21; 95% CI 0.16-0.28 months; P<0.0001), and OS was not achieved vs 66.7 months (HR 0.68; 95% CI 0.49-0.94 months; P=0.0196). After a median follow-up of 59.4 months, G-Clb was also superior to R-Clb (n=330): PFS was 28.9 vs 15.7 months (HR 0.49; 95% CI 0.41-0.58 months; P<0.0001), and OS not reached vs 73.1 months (HR 0.76; 95% CI 0.60-0.97; P=0.0245) (Figure 3). In addition, the median time to next treatment for G-Clb was almost 22 months longer than with R-Clb: 56.4 vs 34.9 months (HR 0.58; 95% CI 0.46-0.73 months; P<0.0001). Therefore, the authors concluded obinutuzumab plus chlorambucil is first choice for first-line treatment of CLL patients with comorbidity.

Vitamin D deficiency and Hodgkin's lymphoma

According to a prospective study by the German Hodgkin Study Group (GHSG), vitamin D deficiency is associated with a poorer outcome in patients with Hodgkin's lymphoma (HL) [4]. In a wide range of cancers, vitamin D deficiency appears to be associated with a poorer prognosis. Yet, for HL, no data were available up to now on vitamin D and patient characteristics and outcomes.

The GHSG recruited 2,653 patients with all stages of HL from the GHSG studies HD7, HD8, and HD9. A pre-treatment serum sample was available from 354 patients. Vitamin D was categorised according to the guidelines of the Institute of Medicine's, Food and Nutrition Board, which define <30 nmol/L as deficient, 30 to 50 nmol/L as insufficient, and ≥ 50 nmol/L as sufficient.

Vitamin D could be determined in 351 of the 354 patients. Vitamin D levels appeared to be independent of tumour mass, clinical condition, and received treatment. Vitamin D values were strongly dependent on the season in which the diagnosis was made. Patients with disease progression or recurrence appeared to have a lower vitamin D level at diagnosis than patients without relapse (21.4 vs 35.5 nmol/L) and were more often deficient (68% vs 41%, P<0.0001). After a median follow-up of 156 months, a lower 5-year progression-free survival was found in patients with a deficit compared to non-deficient patients (74.4% vs 84.6%) (Figure 4). Patients with a deficiency had almost twice the risk of death compared to patients without a deficiency (HR 1.82; 95% CI 1.53-2.15; P<0.0001). Vitamin D supplementation is safe and inexpensive and might improve the results of deficient HL patients, according to the authors. A randomised intervention should confirm this.

Survival of very elderly patients with diffuse large B-cell lymphoma

A Swedish lymphoma registry study revealed that anthracycline-based treatment with curative intention is also associated with improved survival in very elderly patients (≥80 years of age) [5]. Furthermore, it showed that the

proportion of patients treated with curative intention varies between different healthcare regions in Sweden, suggesting different routines when it comes to treating the very elderly. Several studies have confirmed that rituximab combined with chemotherapy is the best treatment option for diffuse large B-cell lymphoma (DLBCL), but few randomised trials have 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. Doctors always have to consider the individual patient's comorbidity and risk of complications.

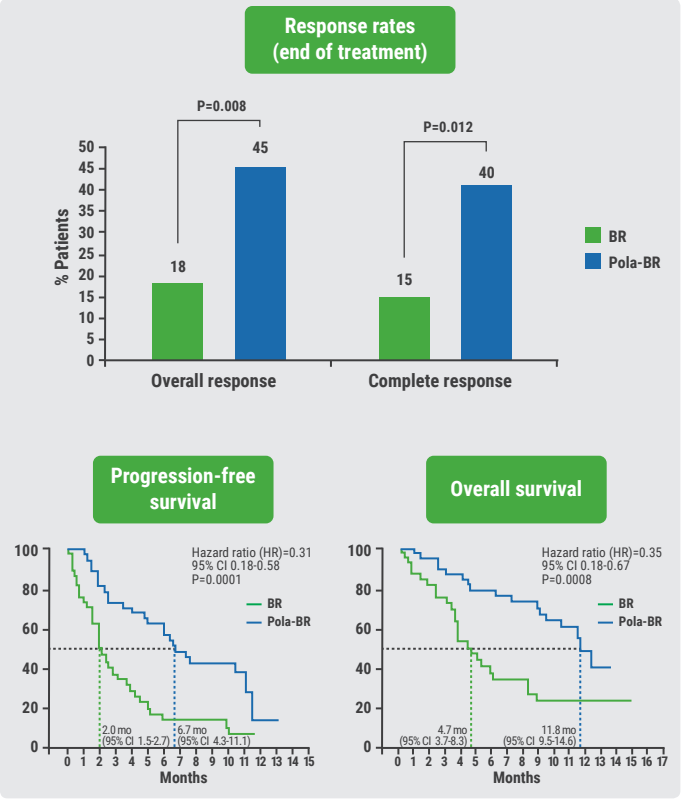
In the nationwide population study, data were analysed on diagnosis, clinical factors and therapy, and survival status of all patients ≥80 years diagnosed with DLBCL in Sweden from 2007 through 2012. In total, 799 patients were identified. Patients treated with anthracycline-based treatment with curative intention (R-CHOP-21, R-CHOP-14, R-CHOEP) showed significantly better survival (HR 2.5; 95% CI 2.2-3.0) compared with patients treated with palliative regimens or no chemotherapy at all. In the regional analysis, 2 regions treated a relatively large proportion of their elderly patients with curative intent (58% in total), whereas 3 regions showed a lower fraction (43% in total), and 1 region deviated with a considerably low percentage (33%). 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).

Promising results for polatuzumab vedotin in DLBCL

Polatuzumab vedotin (pola), added to bendamustine plus rituximab (BR), has again shown promising results in patients with diffuse large B-cell lymphoma (DLBCL) [6]. Pola is an antibody-drug conjugate that targets CD79b, a protein that is expressed in, for example, DLBCL. Based on the first results of the GO29365 study, pola recently obtained the status Breakthrough Therapy from the American FDA, and PRIority MEdicines (PRIME) status from the European EMA for the treatment of refractory/recurrent DLBCL. At EHA 2018, the safety and efficacy data of the randomised FL and DLBCL cohorts of this worldwide phase 1b/2 study were shown.

In the study, 80 FL and 80 DLBCL patients who were not eligible for a stem cell transplantation were randomised 1:1 to 6 cycles of pola plus BR or BR alone. In the FL arms, complete response rates based on PET scans (PET-CR) and PFS were

Figure 5 Polatuzumab vedotin added to bendamustine plus rituximab (BR) in patients with diffuse large B-cell lymphoma [6]



comparable. In patients with recurrent/refractory DLBCL, pola-BR appeared to reduce the risk of disease progression and death compared to treatment with BR alone. At the end of treatment, 40% of patients who received pola-BR achieved a complete response (PET-CR) compared with 15% of patients treated with BR alone (P=0.012). In addition, the median PFS tripled (6.7 vs 2.0 months; HR 0.31; P<0.0001) and OS more than doubled (11.8 vs 4.7 months; HR 0.35; P=0.0008) in patients treated with pola-BR compared with BR (Figure 5).

Ibrutinib plus rituximab in Waldenström's macroglobulinemia

The iNNOVATE study showed that the combination ibrutinib plus rituximab is superior to treatment with rituximab alone in patients with Waldenström's macroglobulinemia (WM) in terms of response and PFS. This applies to both untreated and previously treated patients [7].

The oral inhibitor of BTK, ibrutinib, is approved in the United States for the treatment of adults with WM and in the EU for the treatment of adults previously treated for WM or adults with untreated WM who are not eligible for chemotherapy. Rituximab is also used in the treatment of WM, alone or

in combination with other agents. In this international, randomised phase 3 study, investigators compared a treatment with ibrutinib plus rituximab with placebo plus rituximab.

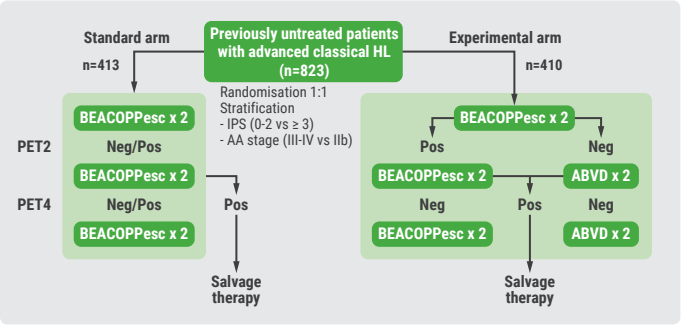
Of the 150 participants, 38% had a high IPSSWM risk score and 45% had not previously been treated for WM. After a median follow-up of 26.5 months, the combination of ibrutinib plus rituximab was found to prolong the PFS compared with rituximab alone (median PFS: not achieved vs 20 months, respectively). This resulted in a 5-fold reduction in the risk of disease progression or mortality (HR 0.20; 95% CI 0.11-0.38; P<0.0001). PFS after 30 months was 82% vs 28%. Improvements in PFS were observed in the various subgroups, including previously untreated patients (HR 0.34; 95% CI 0.12-0.95), patients with relapsed disease (HR 0.17; 95% CI 0.08-0.36), patients with MYD88L265P/CXCR4WT mutations (HR 0.17; 95% CI 0.06-0.49), patients with MYD88L265P/CXCR4WHIM mutations (HR 0.24; 95% CI 0.09-0.66), and patients with MYD88WT/CXCR4WT mutations (HR 0.21; 95% CI 0.04-1.1). Overall (≥ molecular response) and major (≥ partial remission) response rates were significantly higher in the ibrutinib/rituximab group than in the rituximab group (92% vs 47%; P<0.0001, and 72% vs 32%; P<0, 0001).

Early PET driven treatment Hodgkin's lymphoma

Six cycles of BEACOPP provides a better long-term disease control than ABVD in advanced Hodgkin's lymphoma but is also associated to more frequent haematological toxicity and a higher risk of myelodysplasia/acute leukaemia and infertility. The final analysis of the randomised, phase 3 AHL2011 study demonstrated that a de-escalation treatment with a switch from BEACOPP to ABVD is possible after two cycles of BEACOPP in most patients (84%) who reach a negative PET after 2 cycles of BEACOPP (PET2) maintaining the same level of disease control and drastically reducing the risk of treatment toxicity compared to patients who received the standard 6 cycles of BEACOPP [8].

In the French study, 823 patients were randomised 1:1 to the standard treatment not adapted by PET delivering 6 cycles of BEAesc (arm A) or the PET-driven strategy

Figure 6 Study design AHL2011 study [8]



(arm B). PET2 positivity rate was similar in arms A (12%) and B (13%) (Figure 6). Based on PET2 results, 346 (84%) patients received 4 cycles of ABVD, and 51 (12%) patients received 4 additional cycles of BEAesc in the experimental arm. The treatment toxicity was significantly higher in patients receiving 6 cycles of BEAesc compared to those who received 2 cycles of BEAesc + 4 cycles of ABVD, with more frequent grade ≥3 adverse effects (anaemia [11% vs 2%], leukopenia [85% vs 74%], thrombocytopenia [44% vs 15%], and sepsis [7% vs 3%]). A total of 204 serious adverse events related to treatment occurred in 119 (26%) patients treated with 6 cycles of BEAesc (leading to death in 6 cases), compared to 102 serious adverse events (leading to death in 2 cases) in 62 (17%) patients treated with 2 x BEAesc plus 4 x ABVD (P<0.003). With a median follow-up of 50 months, the estimated 4-year PFS was similar in the standard (87.4%) and the PET-driven arms (87.1%; P= 0.68). OS was similar in both arms.

So, without any new drug, this approach based on the early response assessment using PET improved the management of patients with advanced Hodgkin's lymphoma, providing a better balance tolerability/efficacy of BEACOPP-based treatment and a better patient outcome than ABVD, Dr Olivier Casasnovas (University Hospital of Dijon, France) concluded.

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Multiple Myeloma

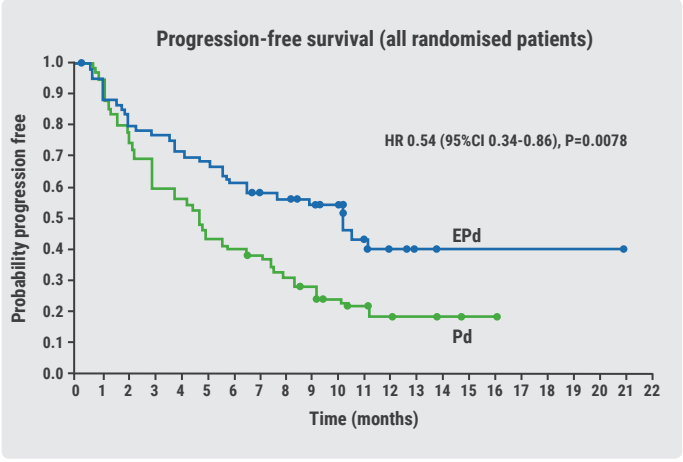
Another hopeful result of CAR T-cell therapy was shown for patients with pre-treated multiple myeloma (MM), in a study on bb2121 anti-BCMA CAR T-cell therapy. Also, the ELOQUENT-3 study has come to a close, and final results were presented.

New treatment option: elotuzumab plus pomalidomide/dexamethasone in RRMM

In the phase 2 ELOQUENT-3 trial, the first randomised trial of elotuzumab plus pomalidomide/dexamethasone (EPd) for patients with relapsed and refractory multiple myeloma (RRMM), EPd showed a 46% reduction in risk of progression or death vs pomalidomide/dexamethasone (Pd), while safety was consistent with prior reports of elotuzumab and pomalidomide. Therefore, EPd may be a new treatment option for RRMM [1].

The immunomodulatory drug pomalidomide/dexamethasone is indicated for RRMM patients who are previously treated with lenalidomide and a proteasome inhibitor. In the phase 3 ELOQUENT-2 study, elotuzumab plus lenalidomide/dexamethasone showed progression-free survival (PFS) benefit and acceptable safety in patients with RRMM. As elotuzumab and pomalidomide may have synergistic effects similar to elotuzumab and lenalidomide, the researchers combined elotuzumab and Pd in the ELOQUENT-3 trial.

Figure 7 ELOQUENT-3 study: progression-free survival elotuzumab plus pomalidomide/dexamethasone vs pomalidomide/dexamethasone in patients with RRMM [1]



In total, 117 RRMM patients were randomised 1:1 to EPd (n=60) or Pd (n=57) and treated in 28-day cycles until disease progression or unacceptable toxicity. At data cut-off, after a minimum follow-up of 9.1 months, 40% (24/60) of the patients in the EPd group and 20% (11/55) in the Pd group were still being treated. The EPd arm showed a 46% lower risk of disease progression or mortality compared to the Pd arm (HR 0.54; 95% CI 0.34-0.86; P=0.0078). The median PFS was 10.3 months (95% CI 5.6 months - not measurable) in the EPd arm, and 4.7 months (95% CI 2.8 - 7.2 months) in the Pd arm (Figure 7). The objective response rate was 53% (95% CI 40-66%) in the EPd arm vs 26% (95% CI 16-40) in the Pd arm (OR 3.25; 95% CI 1.49-7.11; P=0.0029). The median number of cycles was 9 in the EPd group and 5 in the Pd group. Despite this longer exposure, grade 3-4 neutropenia (EPd 13% vs Pd 27%) and anaemia (10% vs 20%) occurred less often in the EPd arm.

Anti-BCMA CAR T-cell therapy bb2121 in pre-treated multiple myeloma

The anti-BCMA CAR T-cell therapy bb2121 has demonstrated substantial activity in heavily pre-treated patients with MM [2]. bb2121 is a second-generation CAR T-cell therapy targeting B-cell maturation antigen (BCMA) to redirect T cells to recognise and kill malignant myeloma cells. Initial data from the dose-escalation phase of CRB-401, a first-in-human study of bb2121 in RRMM, has shown promising efficacy and safety. Patients in the dose-escalation had received ≥

Table 1 Safety data of anti-BCMA CAR T-cell therapy bb2121 in patients with pre-treated multiple myeloma [2]

	All infused patients (n=43)	
TEAE, n (%)	Overall	Grade ≥3
CRS[a]	27 (63)	2 (5)
Neurotoxicity[b]	14 (33)	1 (2)
Neutropenia	35 (81)	34 (79)
Thrombocytopenia	26 (61)	22 (51)
Anaemia	24 (56)	19 (44)
Infection[c]		
Overall	26 (61)	9 (21)
First Month	10 (23)	2 (5)

[a] Cytokine Release Syndrome, CRS uniformly graded per Lee DW, et al. Blood 2014, 124;188-95.
[b] Events occurring in first 28 days
[c] Including SOC infections and infestations

3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or were double refractory, and had ≥50% BCMA expression on plasma cells. In the dose-expansion phase, patients had to have received daratumumab and been refractory to their last line of therapy; no BCMA expression was required. Following lymphodepletion with fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) given daily for 3 days, patients received 1 infusion of bb2121.

Updated results from 43 patients after 5 more months of follow-up show that bb2121 remains generally well tolerated while inducing deep and durable responses in patients with advanced MM (Table 1). The median PFS among 18 patients treated with active doses in the dose escalation cohort was 11.8 months and a 96% overall response rate was reported in 22 patients treated with >150 × 106 CAR T cells. Additionally, an unprecedented rate of minimal residual disease (MRD) negativity was observed, with 100% of 16 evaluable responders achieving MRD negativity. Comparable activity was observed in patients with low (<50%) vs high (≥50%) BCMA-expressing myeloma (overall response rate of 100% vs 91%, respectively). Results from this ongoing study are informing the global pivotal phase 2 trial (KarMMaTM) in patients with RRMM, which is now open for enrolment in North America and Europe.

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Stem Cell Transplantation and Special Therapy

For many patients with blood malignancies, a haematopoietic stem cell transplantation (HSCT) remains the best therapeutic option. Numerous studies are being done to improve outcomes of these transplantations and to reduce the burden of acute and chronic graft vs host disease, in particular by the *European Group for Blood and Marrow Transplantation* (EBMT). This chapter covers the results of four of these studies. Three are from the *Acute Leukemia Working Party* (ALWP) about minimal residual disease (MRD) in AML; a risk score that predicts the survival of AML patients after autologous stem cell transplantation (ASCT); and about limited chronic graft-versus-host-disease (GVHD), which showed to be associated with lower risk of AML relapse. The fourth is a study from the *Lymphoma Working Party* (LWP) about transplantation in HL now and then.

Minimal residual disease in AML in CR2 pre-allogeneic stem cell transplantation

A study of the *Acute Leukemia Working Party* (ALWP) of the EBMT showed that achieving a negative minimal residual disease (MRD) status after second-line treatment for relapsed AML is associated with lower relapse rates and improved leukaemia-free survival (LFS) after allogenic stem cell transplantation (SCT) [1]. These observations are similar to the effect of MRD status in the frontline setting, explains Prof. A. Nagler, former chair of the ALWP EBMT. Therefore, MRD status pre-SCT for AML relapsing patients achieving complete remission (CR)2 should dictate therapeutic strategies in this patient population.

The current definition of CR in patients with AML is based on recovery of normal blood counts after treatment and morphological assessment of the marrow. However, patients in CR can still harbour a significant number of leukaemic cells that may result in relapse. MRD assessment can establish, by different methods, the presence of 1:10^3- 1:10^6 leukaemia cells. The level of MRD as assessed at particular time-points during AML treatment, and in particular prior to SCT, is an independent and important predictor of outcome. However, most of the existing data are available for CR1 and there is until now limited data on the role of MRD in patients achieving CR2 following leukaemic relapse.

The ALWP retrospectively analysed SCT outcomes in a group of 1,042 patients with *de novo* AML in CR2 given SCT between 2006 and 2016 from human leukocyte antigen-matched siblings (n=719) or 10/10 matched unrelated donors (n=293), who had available MRD status data at the time of SCT and were registered in the data base of the ALWP of the EBMT. In all, 749 patients (72%) were MRD negative and 293 (28%) had positive MRD at the time of SCT. The 2-year relapse rate was 24% (95% CI 21-28) and 40% (95% CI 34-46) in the MRD(-) and MRD(+) groups, respectively (P<0.001). The predicting factors for relapse in multivariate analysis were MRD(-) status (HR 0.57; P<0.001), good cytogenetics (HR 0.62; P=0.001), longer time from diagnosis to SCT (HR 0.97; P<0.001) and *in vivo* T-cell depletion (HR 1.35; P=0.03). The 2-year LFS was 57% (53-61) and 46% (40-52%), respectively (P=0.001). The predicting factors for LFS were MRD(-) status (HR 0.76; P=0.01), good cytogenetics (HR 0.79; P=0.04), and longer time from diagnosis to SCT (HR=0.99; P<0.001). Age, gender, donor, or conditioning type did not predict relapse or LFS rates.

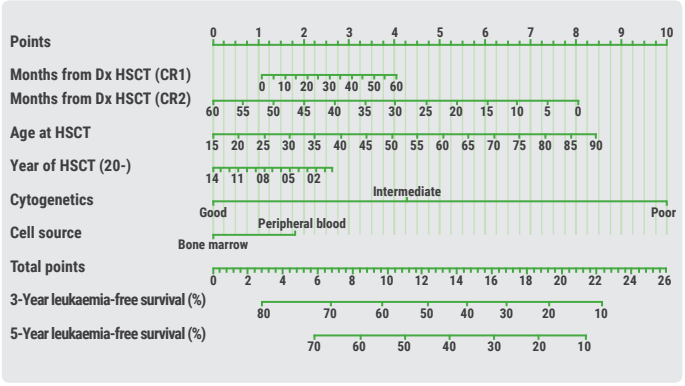
Newly developed risk score of survival in AML after autologous stem cell transplantation

The ALWP of the EBMT developed a first predictive score for patients with AML treated with an autologous stem cell transplantation (ASCT) [2]. The scores for prediction of 3 year and 5 year may help to better define patients who benefit from autologous transplantation as post-remission treatment, the ALWP explained.

Although an ASCT is proposed as consolidation therapy for patients with AML, concerns regarding the risk of relapse has led to decreasing use of this procedure. However, ASCT is associated with reduced non-relapse mortality (NRM) and a better quality of life compared to allogeneic SCT.

A retrospective study analysed data of 2,298 adult AML patients in CR treated with ASCT as consolidation therapy between 2000 and 2015 in EBMT centres. The majority of patients were in CR1 (90%) and had intermediate risk cytogenetics (75%), followed by good (18.5%), and poor (6.5%). Peripheral blood was the cell source in 93% of the cases. Total body irradiation was used as the backbone of conditioning in 86% of the patients. The final variables included in the multivariable model were age, cytogenetic risk group according to the Medical Research Council classification, cell source, year of transplantation, disease status, and time from diagnosis to transplantation as an interaction term.

Figure 8 Risk score survival AML after autologous stem cell transplantation [2]



The cumulative points a patient receives corresponds with 3-year and 5-year LFS probability, described in the bottom rows of Figure 8. Patients in the highest and lowest quartiles had a 60.8% and 27.7% probability of 5-year LFS.

Limited chronic graft-versus-host disease is associated with lower risk of AML relapse

Another retrospective study of the EBMT, again from the ALWP, showed that limited chronic graft-versus-host disease (GVHD) was associated with a lower risk of AML relapse and a trend to a better OS; all other forms of GVHD were associated with lower OS [3].

The efficacy of allogeneic haematopoietic cell transplantation (HCT) in patients with acute AML depends both on chemo/radiotherapy given in the conditioning regimen and on immune-mediated graft-versus-leukaemia (GvL) effects. Previous studies have observed an association between occurrence of acute (a) and chronic (c) GVHD and a lower risk of AML relapse in patients with *de novo* AML. Further, although it is well established that, in comparison to *de novo* AML, secondary AML (sAML) is less sensitive to chemotherapy, its susceptibility to GvL effects has not been studied in large cohorts of patients. Hence, the ALWP analysed this retrospectively. The study population included adult patients with sAML in first or second CR who received a HCT between 2005 and 2016. According to the investigators, previous studies might have overestimated the beneficial impact of GVHD on relapse prevention given the tight association between GVHD and (NRM). Therefore, they assessed the evolution of relapse rate over time according to GVHD condition by calculating the relapse rate per patient-year within sequential 90-day intervals, as previously reported [4].

In total, 3,303 patients met the inclusion criteria. Status at transplantation was CR1 in 2,919 patients (88%) and CR2 in 384 (12%). Of the enrolled patients, 1,517 received grafts from matched siblings, 1,427 from matched unrelated donors (MUD), and 359 from mismatched unrelated donors. 41% of the patients received a myeloablative conditioning, and 49% anti-thymocyte globulin (ATG). Stem cell source was peripheral blood stem cell transplantation in 90% of the patients. The proportion of patients with grade II and III-IV aGVHD was 15% and 10%, respectively. At 2 years, the cumulative incidence of cGVHD was 43% (18% extensive), the cumulative incidence of relapse 30%, and OS 53%. Relapse rates declined gradually over time and were significantly lower in patients with cGVHD than in those without (P=0.009). Grade III-IV aGVHD and cGVHD were each associated with a lower risk of relapse but grade II aGVHD was not. Other factors associated with a lower risk of relapse included absence of poor-risk cytogenetic (P=0.008), myeloablative conditioning vs reduced-intensity (RIC) conditioning (P<0.001), and MUD (P=0.01). Other factors associated with increased mortality included high age (P<0.001), intermediate (P=0.01) and poor (P<0.001) risk cytogenetics, and mismatched unrelated donors (P=0.01).

Transplantation in Hodgkin's lymphoma: now and then

The LWP of the EBMT presented interesting results of a retrospective analysis on transplantation management in patients with relapsed/refractory HL (rrHL) [5]. Transplantation activity, the clinical pattern of patients undergoing this treatment, and the characteristics of the procedure have significantly changed over the study period, and results in terms of OS and NRM for both autologous (auto) SCT and allogeneic (allo) SCT are much better, concludes the LWP.

Both auto-SCT and allo-SCT are well-accepted treatment strategies for patients with relapsed rrHL. Nevertheless, both transplant modalities have evolved over time and the recent advent of new drugs might have modified the indications and timing of SCT. Patients were included in the study if they had primary rrHL and had undergone an auto-SCT as first SCT or an allo-SCT either as a first SCT or after a prior auto-SCT between January 1990 to December 2014. In total, 13,639 patients (11,435 auto-SCT and 2,204 allo-SCT [555 first allo-SCT and 1,649 allo-SCT after an auto-SCT]) were registered in the EBMT database during the study period. The number of auto-SCT steadily increased from 129 in 1990 up to a maximum of 811 in 2010; the number of allo-SCT also increased from 6 in 1990 up to a peak of 243 in 2014.

With regards to autologous recipients, there was a significant increase in age at SCT (31 years in 1990-1994 vs 35 years in 2010-2014), and time between diagnosis and SCT was shorter (31 months in 1990-1994 vs 23 months in 2010-2014). Peripheral blood has become the universally used stem cell source (30% in 1990-1994 vs 98% in 2010-2014) and total body irradiation has almost been abandoned (4% in 1990-1994 vs 1.7% in 2010-2014). The 36-month OS has significantly improved over time (63% in 1990-1994 vs 79% in 2010-2014), as well as NRM (12% in 1990-1994 vs 6% in 2010-2014). Interestingly, allo-SCT has been less used as the first SCT (88% in 1990-1994 vs 23% in 2010-2014), whereas the number of allo-SCT after a first auto-SCT has steadily increased (12% in 1990-1994 vs 77% in 2010-2014).

Time between diagnosis and SCT has also decreased over time in allogeneic recipients (36 months in 1990-1994 vs 34 months in 2010-2014). Performance status >80% at SCT has improved (62% in 1990-1994 vs 94% in 2010-2014). Also, in allo-SCT peripheral blood has become the universal source of stem cells (6% in 1990-1994 vs 84% in 2010-2014), and there has been a more frequent use of reduced intensity conditioning protocols (0% in 1990-1994 vs 70% in 2010-2014), as well as of matched unrelated and haploidentical donors (0% in 1990-1994 vs 48% in 2010-2014, and 0% in 1990-1994 vs 17% in 2010-2014, respectively). The 36-month OS estimates have also significantly improved (21% in 1990-1994 vs 61% in 2010-2014), as well as those for PFS (15% in 1990-1994 vs 43% in 2010-2014) and NRM (58% in 1990-1994 vs 22% in 2010-2014).

Improvement of supportive measures as well as in the experience of the transplant centres and a better selection of patients could account for these changes, suggested the authors. Unfortunately, the impact of the introduction of new treatment options, such as checkpoint inhibitors, is difficult to ascertain at this point.

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Benign Haematology

Improvement of treatment and knowledge of blood diseases can substantially increase patient's quality of life. For instance, the new drug ravulizumab for the treatment of paroxysmal nocturnal haemoglobinuria (PNH), administered by intravenous infusion only once every 8 weeks, showed to be as effective and safe as eculizumab, given once every 2 weeks. Another study concluded that low-dose rituximab is more cost-effective than the current standard dose in patients with primary immune thrombocytopenia (ITP). And finally, at the Presidential Symposium investigators showed that transfusions suppress inflammation, which may predispose transfused patients to severe infections, eventually leading to organ failure.

Ravulizumab only once every 8 weeks for paroxysmal nocturnal haemoglobinuria

In patients with paroxysmal nocturnal haemoglobinuria (PNH), ravulizumab once every 8 weeks has shown noninferiority to eculizumab once every 2 weeks [1]. Both drugs are C5 inhibitors, but ravulizumab has a half-life that is 3 to 4 times longer than that of eculizumab; a big advantage for patients, the investigators emphasised.

The results come from a phase 3, open-label, multicentre study and were presented as late breaking abstract. A total of 285 PNH patients who had not previously been treated with complement inhibitors were randomised 1:1 to receive ravulizumab (n=125) or eculizumab (n=121). All patients demonstrated at least one PNH-related symptom and levels of lactate dehydrogenase (LDH) 1.5 times the upper limit of normal at screening. Noninferiority was declared if the lower bound of the 95% CI for difference in proportion of patients with transfusion avoidance (proportion of patients who remain transfusion-free) receiving ravulizumab vs eculizumab was > -20% and lower bound of the 95% CI for odds ratio for LDH normalisation (LDH upper limit of normal = 246 U/L) between ravulizumab vs eculizumab was >0.39.

All patients, except for 2 in the eculizumab arm, completed the treatment period of 26 weeks. Ravulizumab was noninferior to eculizumab in proportions of patients achieving transfusion avoidance (73.6% vs 66.1%; difference 6.8%; 95% CI -4.7-18.1) and LDH normalisation (53.6% vs 49.4%, OR 1.19; 95% CI 0.80-1.77). The most frequently reported adverse event was headache (36.0% vs 33.1% in patients receiving ravulizumab vs eculizumab). Serious adverse events were experienced by 8.8% vs 7.4% in patients receiving ravulizumab vs eculizumab. Major adverse vascular events occurred in 2 patients receiving ravulizumab, and 1 patient receiving eculizumab.

Low-dose rituximab more cost-effective in patients with immune thrombocytopenia

Data from the UK ITP registry show that a low dose of 100 mg rituximab is as effective as the standard dose of 375 mg/m^2 in improving platelet count and achieving partial remission in patients with primary immune thrombocytopenia (ITP) [2]. Both doses are equally effective in reducing bleeds with no difference in the median time to next treatment. Thus, 4 weeks of 100 mg rituximab weekly is a more cost-effective option than the standard dosing regimen of 4 weeks of 375 mg/m^2 weekly.

In the past, the efficacy of lower doses of rituximab (<375 mg/m^2) has been shown, but there have been no large-scale, comparative, randomised trials. Hence, British investigators performed a retrospective review of the efficacy of two main dosing regimens in ITP patients. They used data from the UK Adult ITP registry, a large national registry of primary ITP. There were 301 patients with sufficient data input for analysis. Of these 301 patients, 179 had received low-dose rituximab and 122 had received standard dose.

The median platelet count was not significantly different at 2, 4, and 6 months after rituximab therapy between the low and standard doses (46, 72, 74 x10^9/L vs 43, 65, 81 x109/L, respectively). However, the authors noticed some ongoing increase in platelet count between 2 and 4 months for both dosing schedules, showing ongoing delayed response. At 2 months after therapy, complete remission (defined as platelets >100 x 10^9/L) was achieved in 21.1% and 32% patients in the low dose and standard dose regimes respectively. This increased to 37.7% and 43.1% at 6 months. Partial remission at 2 months was achieved in 36% and 27.1% patients for 100 mg and 375 mg/m^2 doses. By 6 months this was 34% and

27%, respectively. Bleeding episodes (all bleeds) before and after therapy were reported in 63.7% and 44.7% of patients in the 100 mg dose group, and 63.9% and 39.3% patients in the 375 mg/m^2 group.

Understanding chronic iron overload

Chronic iron overload is common in thalassemia, sickle cell disease, and myelodysplastic syndromes, due to red blood cell transfusions and increased intestinal iron absorption to support ineffective erythropoiesis. German researchers studied the impact of transfusions on the phenotypic plasticity of monocytes and macrophages and their responses to infectious cues, i.e. whether iron accumulation in these three different pathologic conditions causes macrophage inflammation and the production of inflammatory molecules. Their results, presented at the EHA Presidential Symposium, showed that transfusions indeed suppress inflammation [3]. This effect may predispose transfused patients to severe infections, which may eventually lead to organ failure. On the contrary, free haem and iron have an inflammatory action on macrophages, which is worsened during infections. This effect causes chronic inflammation and tissue damage in sickle patients and patients treated with iron.

They concluded that different forms of iron accumulation in macrophages (red blood cells vs free haem and iron) in different diseases show opposite effects on inflammation. The data suggests that molecules able to bind iron have therapeutic benefit on these diseases through the modulation of these processes. Finally, these results suggest that transfusion practice might increase the risk of infections not solely by promoting the growth of microorganisms through increasing iron availability, but also by impairing the innate immune system through the alteration of macrophage plasticity. The underlying mechanisms are currently under investigation.

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Paediatric Haematology

Paediatric haematology is a divers and complex field. In recent years, more knowledge about causalities and treatment options has become available. This year, for instance, real-world data showed that the prognosis of children with relapsed or refractory AML has significantly improved. Also, the results of CD22 CAR T-cell therapy in children with B-cell acute lymphoid leukaemia (ALL) are promising. Further, novel insights of spleen injury in infants with sickle cell anaemia can predict and perhaps prevent acute splenic sequestration crisis.

Improved outcome in children with relapsed acute myeloid leukaemia

Children with relapsed or refractory AML have a reasonable option to be cured with intensive second and third line therapy, concluded European researchers in a prospective population study [1]. The prognosis of paediatric patients with AML improved in recent decades. However, it is not yet clear what factors have contributed to this improvement. Hence, the researchers set up a prospective study in which 435 children with relapsed (n=395) and refractory (n=43) AML were followed between 2009 and 2016 from Germany, Austria, Czech Republic, Switzerland, Poland, Italy Slovakia, Belgium, and the Netherlands.

Most patients (89%) had been treated with the recommended re-induction therapy consisting of liposomal daunorubicin/fludarabine/cytarabine (L-DNR-FLA) followed by FLA course. The event-free survival (second EFS) and OS 3 years after relapsed/refractory AML were 42% and 51%, respectively. These data show a remarkable improvement compared to both second EFS and OS of children enrolled in the international Relapse AML 2001/01 trial (second EFS 33%; OS 38%; P<0.005). Duration of first remission and genetic lesions remain significant prognostic factors. Remission <1 year vs >1 year: second EFS 32% vs 57%; OS 36% vs 60% (P<0.00001); and core binding leukaemia vs others: second EFS 57% vs 31;

OS 61% vs 37% (P<0.0001). Third line therapy including second SCT (12%) was applied more often with a curative intention compared to the international Relapse AML 2001/01 trial: EFS was 42% vs 18% (P<0.001). In her presentation, Dr Mareike Rasche (University Hospital Essen, Germany) emphasised the need for further research to identify children who will relapse earlier, to apply more effective therapy, or to treat patients early in case of a molecular relapse. Furthermore, prospective, randomised trials are urgently needed to identify the best conditioning regimen.

Promising results of CD22 CAR T-cell therapy for children with B-cell ALL

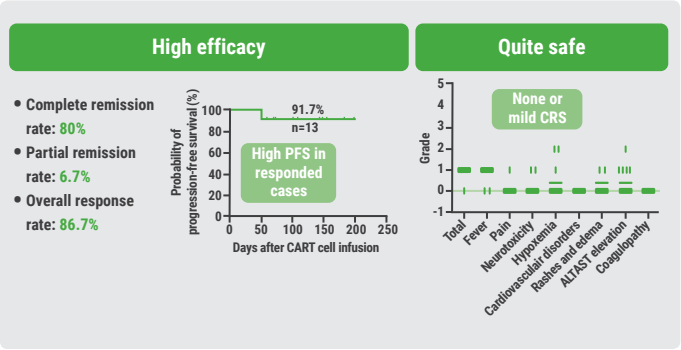
CD22 CAR T-cell therapy has been shown to be an effective and safe treatment option for children with refractory/recurrent B-cell acute lymphocytic leukaemia (B-ALL), even when allogeneic SCT and CD19 CAR T-cell therapy have failed [2]. B- ALL is usually treated with chemotherapy or allogeneic SCT. CD19 CAR T-cell therapy has also been shown to be successful in patients with refractory/recurrent ALL. However, a significant proportion of patients regress within a year after successful CD19 CAR-T cell therapy. Thus there is an urgent need for new treatment options.

Investigators evaluated CD22 CAR T-cell therapy in 15 children with refractory/recurrent B-ALL, for whom multiple treatment lines failed, including allogeneic SCT and CD19 CAR T-cell therapy. The treatment was effective with an overall response rate of 86.7% and a CR rate of 80.0% (Figure 9). Six patients underwent allogeneic SCT after CD22 CAR T-cell therapy. The PFS at 6 months was 91.7%; 1 patient had a relapse on day 50. Side effects were mild, and none of the patients died due to side effects.

Novel insights into spleen injury during the first 2 years of life in SCA children

In children with sickle cell anaemia (SCA), spleen dysfunction can occur as early as 4 months of age. In addition, irreversibly sickled cells (ISCs) are a predictive marker of acute splenic sequestration crisis (ASSC), a condition that greatly contributes to spleen loss of function [3]. That can be concluded from a longitudinal study in a cohort of 47 infants with SCA enrolled at 3 to 6 months and followed-up to 24 months.

Figure 9 Efficacy and toxicity CD22 CAR T-cell therapy in children with B-cell ALL [2]



In SCA, the spleen is the first organ to be injured; notably, because impaired deformability and/or adhesion of sickled red blood cells promote their sequestration. Moreover, ASSC, a life-threatening complication, happens in 10-30% of SCA infants, with 75% of first cases occurring before the age of 2 years. Determinants, predictive factors and consequences of ASSC are not established. At enrolment, the presence of ISCs was 0.96% with a significant increase of ISCs at 18 months (1.61%). The ASSC group showed significantly higher ISCs at enrolment than the ASSC-free group (1.61% vs 0.54%). ISCs seem to appear in the circulation before the occurrence of an ASSC, indicating a potential role as a predictive marker of ASSC.

Abnormal adhesion of red blood cells to the spleen matrix in the open microcirculation might be another factor causing splenic injury. In particular, the spleen is lined with laminin, a known ligand for Lu/BCAM. We observed an increase in the expression and activation of Lu/BCAM with time. The investigators observed a significant increase in the number of adherent red blood cells on laminin-coated channels between enrolment and 24 months (990 RBCs/mm^2 vs 1787 RBCs/mm^2, respectively). However, they observed no difference with respect to Lu/BCAM adhesion, expression and activation properties when comparing the ASSC group and the ASSC-free group.

References

1. Rasche M, et al. EHA 2018, S119.
2. Pan J, et al. EHA 2018, S832.
3. El Hoss S, et al. EHA 2018, S1589.