Haemostatic abnormalities associated with mortality in patients with COVID-19

Presented By

Dr Yu Hu, Wuhan Union Hospital, China

Conference

EHA 2021

COVID-19 causes a variety of abnormalities in thrombosis and haemostasis. Several studies have demonstrated that the severity grade of coagulopathies is significantly associated with the severity of COVID-19 disease progression and mortality.

COVID-19 is a systemic infectious disease affecting various organ systems and thus causes a broad variety of symptoms, including haematological abnormalities, such as thrombosis, embolism, and petechiae [1]. In a single centre, retrospective study (n=380) of complications of non-survivors (n=55), acute respiratory distress syndrome was present in 69%, septic shock in 20%, disseminated intravenous coagulation in 14.6% and venous thromboembolism in 5.45% [2]. Dr Yu Hu (Wuhan Union Hospital, China) discussed these coagulopathies in COVID-19 in further detail [3].

Dr Hu noted that patients with fatal COVID-19 had a significantly higher level of D-dimer compared with COVID-19-survivors, as well as increased activated partial thromboplastin time (aPTT;), increased prothrombin time (PT), and decreased fibrinogen levels. Results from a meta-analysis evaluating 24 studies showed that at baseline, PT values were significantly associated with risk stratification and prognosis and D-dimer at baseline was associated with stratification [4].

Furthermore, platelet count was significantly decreased in patients who died from COVID-19. The incidence of thrombocytopenia in non-survivors (n=55) was 63.6% versus 15.3% in survivors (n=176). Three studies from China indicated that the nadir platelet count was associated with the risk of in-hospital death, with 92.1% mortality in patients with 0–50 platelets $x10^9$/L and 61.2% mortality in patients with 50–100 platelets $x10^9$/L at nadir platelet count [5-7]. The incidence of disseminated intravenous coagulation was also associated with disease severity and mortality [4].

Mechanisms of COVID-19-associated coagulopathy include systematic inflammation, endothelial dysfunction (by direct infection and secondary damage) and platelet activation (SARS-CoV-2 directly binds and enhances platelet activation *in vitro*).

In summary, coagulopathy is one of the important causes of death in COVID-19 patients and should be closely monitored by clinicians. Given the various haematological abnormalities in COVID-19, timely therapeutic intervention with anticoagulant therapy could improve prognosis.

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6. **Liu Y, et al. Platelets 2020;31(4):490-496.**
7. **Zhao X, et al. EPMA Journal 2020;11(2):1-7.**

The discovery and diagnosis of COVID-19 vaccine-induced immune thrombotic thrombocytopenia

Presented By

Prof. Sabine Eichinger, Medical University Hospital of Vienna, Austria

Conference

EHA 2021

The history of the first diagnosis of vaccine-induced immune thrombotic thrombocytopenia after receiving a COVID-19 vaccine was presented, as well as updated patient characteristics from Europe and Canada. To aid diagnosis, the acronym VITT can be used: Vaccine, Interval, Thrombosis, Thrombocytopenia. Treatment recommendations were presented as well.

Prof. Sabine Eichinger (Medical University Hospital of Vienna, Austria) presented the discovery of vaccine-induced immune thrombotic thrombocytopenia (VITT) as well as algorithms for diagnosis and treatment [1]. The first diagnosed case of VITT was a 49-year old woman. On 17 February 2021, she received the first COVID-19 vaccine (ChAdOx1 nCov-19, AstraZeneca) and mild side effects resolved after 2–3 days. From day 5, there was increasing abdominal pain, chills, and vomiting. On the morning of day 10, the patient was admitted to the hospital. She had a low platelet count and elevated D-dimer. Computer tomography (CT) imaging showed portal vein thrombosis and peripheral pulmonary embolism. Because of high fibrinogen levels, she received enoxaparin in the evening of day 10. On day 11, she had massive abdominal pain. A repeat CT showed progression of portal vein thrombosis, and small thrombi in the infrarenal aorta and both iliac arteries. Laboratory results were similar to day 10. The patient died on the evening of day 11. Autopsy showed cerebral thrombosis in addition to medical findings.

Several differential diagnoses were considered and dismissed: COVID-19, disseminated intravascular coagulopathy, antiphospholipid syndrome, thrombotic thrombocytopenic purpura, and heparin-induced thrombocytopenia. Platelet activation tests of 4 patients with suspected VITT finally led to the discovery of VITT. Serum of suspected VITT patients was spiked with normal platelets and platelet factor 4, which led to strong platelet activation [2].

Prof. Eichinger also presented updated patient characteristics. While in mainland Europe the majority of patients were women (≥80%) and a maximum of 54 years old [2,3], only 57% of patients in the United Kingdom were women and they were up to 77 years of age [4]. First reported cases from Canada are in line with British findings.

To aid diagnosis, the acronym VITT can be used: Vaccine (AstraZeneca, Johnson&Johnson/Janssen), Interval (symptoms 5–10 days after vaccination), Thrombosis, Thrombocytopenia. Specific assays have also become available. Treatment recommendations include:

- Avoid heparin use in suspected VITT; instead, use alternative anticoagulants (argatroban, danaparoid sodium, and direct oral anticoagulants).
- Consider intravenous immunoglobulin.
- Avoid platelet transfusions and vitamin K antagonists during acute thrombocytopenia.

In conclusion, the diagnosis of VITT and supporting diagnostic tools have improved over the last few months. However, typical characteristics of patients at risk and predictive factors remain unknown to date.

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2. **Greinacher A, et al. N Engl J Med. 2021;384:2092-101.**
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Immuno-oncology agents effective in treating classic Hodgkin's lymphoma

Presented By

Prof. Marc André, Centre Hospitalier Universitaire UCL Namur, Belgium

Conference

EHA 2021

Trial

CheckMate 205; KEYNOTE-087; NIVAHL

Checkpoint inhibitors are effective and well-tolerated in patients with refractory or relapsing Hodgkin-lymphoma. Several clinical trials also showed encouraging outcomes in patients with previously untreated, unfavourable Hodgkin's lymphoma.

Prof. Marc André (Centre Hospitalier Universitaire UCL Namur, Belgium) discussed the use of checkpoint inhibitors in refractory or relapsing (r/r) classic Hodgkin's lymphoma (cHL) post-brentuximab vedotin (BV)/autologous hematopoietic stem cell transplantation (ASCT) and pre-ASCT, as well as first-line treatment of advanced and localised cHL [1].

Recent clinical studies in r/r cHL include:

- The CheckMate 205 study (**NCT02181738**)
  - Nivolumab was tested in BV-naïve patients, in BV after ASCT-treated patients, and in BV before and/or after ASCT-treated patients.
  - Overall response rate (ORR) was 69%, with 16% complete response (CR) and 53% partial response. Progression-free (PFS) and overall survival (OS) were reduced in patients with progressive disease.
  - Safety outcomes were favourable, with grade 3/4 adverse events (AEs) in only ≥2% of patients [2].
- The KEYNOTE-087 study (**NCT02453594**)
  - Pembrolizumab was tested in patients with r/r cHL who were either BV-treated/post ASCT, BV-naïve/post, or patients in which chemotherapy and BV had failed.
  - Complete response was achieved in ≤18.3%, median PFS was 13.6 months. Overall survival was 86.4% after 36 months. The primary endpoint ORR was 71.0%.
  - Safety outcomes were acceptable; no grade 5 AEs occurred [3].
- Checkpoint inhibitors before ASCT (**NCT02572167**):
  - BV plus nivolumab were administered in patients with r/r cHL, who received ASCT per investigator discretion.
  - PFS was 77% after 36 months, and OS at 36 months was 93%.
  - Side effects were mild; only 2 patients discontinued due to AEs [4].

Prof. André also presented the trials examing the use of these agents as first-line treatment:

- The CheckMate 205 study
  - A 4th cohort of adults with newly diagnosed, untreated, advanced-stage cHL received nivolumab as monotherapy followed by combination therapy with AVD (i.e. doxorubicin, vinblastine, dacarbazine).
  - ORRs were 69% at the end of monotherapy, 90% after 2 combination cycles, and 84% at the end of therapy, with CR of 18%, 51% and 67%, respectively.
  - Safety results were acceptable [5].
- The NIVAHL study (**NCT03004833**)
  - Sequential therapy of nivolumab monotherapy, combination therapy (nivolumab + AVD), and radiotherapy was assessed in adults with newly diagnosed, untreated, early-stage, unfavourable cHL.
  - The primary endpoint was CR after the end of study treatment, which was ≥87%. One-year PFS was ≥98%.
  - The treatment was well tolerated [6].

In conclusion, anti-PD1 antibodies are now the standard of care in r/r cHL and are safe and effective compounds for first-line treatment. Combination therapies seem to further improve response rates.

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3. **Zinzani PL, et al. Abstract 625, ASH Annual Meeting 2019, 7-10 December.**
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ZUMA-5 vs SCHOLAR-5: Axicabtagene ciloleucel shows significant benefits in follicular lymphoma

Presented By

Prof. John Gribben, Cancer Research UK Barts Centre, United Kingdom

Conference

EHA 2021

Trial

ZUMA-5

Updated results from the ZUMA-5 trial showed that treatment with axicabtagene ciloleucel resulted in significantly higher efficacy in patients with relapsed/refractory follicular lymphoma compared with real-world treatment patterns from the SCHOLAR-5 control cohort. This data supports that axicabtagene ciloleucel-treatment represents a significant improvement in treatment options for these patients.

Prof. John Gribben (Cancer Research UK Barts Centre, United Kingdom) presented updated results of the phase 2 ZUMA-5 study (**NCT03105336**), a prospective, interventional study of axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory (r/r) follicular lymphoma who have failed ≥2 prior lines of therapy [1]. Clinical outcomes from the ZUMA-5 cohort were compared with the international SCHOLAR-5 control cohort to provide comparative evidence in r/r follicular lymphoma patients meeting ZUMA-5 eligibility criteria.

Cross-study comparisons of a retrospective versus a prospective clinical trial may be difficult to interpret or prone to bias. Propensity score weighting methods were used to create balance for a broad set of prognostic covariates. The common dataset included overall response rate (ORR), complete response rate (CR), overall survival (OS), progression-free survival (PFS), time to next treatment (TTNT), and duration of response (DOR).

The SCHOLAR-5 real-world treatment patterns were highly heterogeneous and highlight the lack of uniform treatment options. Experimental treatment options were commonly used in late-line follicular lymphoma treatment. Median follow-up for SCHOLAR-5 was 26.2 months and 23.3 months for ZUMA-5.

Updated efficacy results showed a significantly higher efficacy in ZUMA-5 compared with SCHOLAR-5 in ORR (94.2% vs 49.9%) and CR (79.1% vs 29.9%), favouring axi-cel treatment. Also, PFS was significantly longer in ZUMA-5 (median not reached vs 12.68 months). The same was true for TTNT (median not reached vs 14.43 months) and OS (median not reached vs 59.8 months). Subgroup analysis of efficacy endpoints consistently confirmed overall efficacy results.

In conclusion, after applying propensity score methods, axi-cel demonstrated a substantial improvement in all clinical endpoints in the ZUMA-5 clinical trial when compared with SCHOLAR-5. The substantial benefits seen in this study suggest that axi-cel addresses an important unmet medical need for r/r FL patients.

1. Ghione P et al. A comparison of clinical outcomes from ZUMA-5 (axicabtagene ciloleucel) and the internation SCHOLAR-5 external control cohort in relapsed/refractory follicular lymphoma (r/r FL). P205-4, EHA 2021 Congress, 09–17 June.

Chemo-free regimens: promising alternative treatment options in r/r DLBCL

Expert

Prof. Marco Ladetto, University of Eastern Piedmont, Italy

Journal

LOTIS-2

Conference

EHA 2021

Several novel agents and combinations are under development as alternatives to chemotherapy treatment in relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL). Many new agents are on the horizon, including novel antibodies, CAR-T cell therapy, checkpoint inhibitors, immunotoxins, PI3K inhibitors, novel kinase inhibitors, BiTE, Bcl-2 inhibitors, and BTK inhibitors. [1].

The poor outcomes of chemotherapy in patients with r/r DLBCL create a major unmet medical need for alternative treatment regimes. This is true for both patients who are eligible and patients who are not ineligible for autologous transplant. For example, rituximab plus gemcitabine and oxaliplatin (R-GemOx) in r/r DLBCL patients ineligible for autologous transplantation showed a median progression free-survival time of 5 months and median overall survival of 10 months only [2]. Thus, alternative treatment options are required.

Prof. Marco Ladetto (University of Eastern Piedmont, Italy) discussed the use of non-chemotherapeutic agents in transplant-ineligible r/r DLBCL. Non-chemotherapeutic agents are used either alone, as a rational combination of biologicals, or in combination with chemotherapy. Three interesting treatment options are:

- loncastuximab tesirine, a novel immunotoxin showed durable response and an acceptable safety profile in the phase 2 LOTIS-2 trial (**NCT03589469**) [3],
- glofitamab, a T-cell engaging agent showed durable response in patients with refractory, aggressive B-cell non-Hodgkin lymphoma in a ecent phase 1 trial (**NCT03075696**) [4], and
- the combined use of tafasitamab, an anti-CD19 antibody, plus lenalidomide, an immunomodulatory agent, which synergistic effects led to a median progression-free survival time of 16.2 months [5].

Prof. Ladetto concluded, "Given the modest value of chemotherapy salvage treatments, it is reasonable to explore the value of non-chemotherapeutic agents, either alone or in rational combinations."

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3. **Caimi PF, et al. Lancet Oncol. 2021 Jun;22(6):790-800.**
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Naratuximab emtansine plus rituximab is safe and effective in diffuse large B-cell lymphoma

Presented By

Dr Moshe Yair Levy, Texas Oncology-Baylor Charles A. Sammons Cancer Center, TX, US

Conference

EHA 2021

Trial

Phase 2

The safety and efficacy of naratuximab emtansine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma and other B-cell non-Hodgkin lymphomas were evaluated in a phase 2 study. Results demonstrated high efficacy and a tolerable and manageable safety profile. This treatment regimen could represent a new treatment option for these patients, including heavily pre-treated patients.

Patients with refractory or relapsing (r/r) B-cell non-Hodgkin lymphoma (B-NHL) and particularly r/r diffuse large B-cell lymphoma (DLBCL) who do not qualify as candidates for a stem-cell transplant or CAR-T cell therapy have a poor prognosis. Naratuximab emtansine is a humanised antibody-drug conjugate targeting CD37, a surface marker of B-lymphocytes. A good safety profile with a 22% overall response rate (ORR) was demonstrated previously in a phase 1 monotherapy study in patients with DLBCL (**NCT01534715**) [1].

Dr Moshe Yair Levy (Texas Oncology-Baylor Charles A. Sammons Cancer Center, TX, US) presented a subsequent, open-label, phase 2 study (**NCT02564744**) for naratuximab emtansine plus rituximab in r/r B-NHL and r/r DLBCL patients, consisting of 2 parts [2]. Part 1 consisted of a safety run-in and a run-in expansion. Participants were divided into cohorts: cohort 1 consisted of r/r DLBCL, and cohort 2 consisted of other r/r B-NHLs. All participants in part 1 received 0.7 mg/kg naratuximab emtansine plus 375 mg/m^2 rituximab intravenously every 3 weeks. Part 2 included only DLBCL patients in 2 cohorts with different treatments: cohort A received the same treatment as all patients in part 1. Cohort B received naratuximab emtansine on days 1 (0.4 mg/kg), 8 (0.2 mg/kg), and 15 (0.2 mg/kg), combined with 375 mg/m^2 rituximab on day 1. This cycle was repeated 6 times with possible extension. Patients were followed up for 1 year after the last patient first dose. The primary endpoints were treatment-emergent adverse events (AEs) and ORR. Efficacy was only assessed in patients with DLBCL.

Included in this study were 100 participants, of which 80 had DLBCL and 20 had other B-NHLs. A large proportion of patients were heavily pre-treated and had advanced DLBCL. Treatment-emergent AEs of grade 3 or higher were observed in 81 patients (81%). The most frequently observed grade 3–4 AEs were haematological and manageable; only 8 patients discontinued treatment due to treatment-related AEs. Of the 10 patients with grade 5 AEs, 2 were considered treatment-related.

Efficacy outcomes in all 80 treated DLBCL patients demonstrated an ORR of 44.7% and 31.6% complete responses (CR). In patients with non-bulky DLBCL, ORR was 50.8%; in non-primary refractory patients that were treated at least third-line, ORR was 46.4% and CR was 32.1%. ORR was 50% in each cohort, with a CR rate of 43.3% in cohort A and 33.3% in cohort B. After a median follow-up of 15 months, the median duration of response was not reached; 66% of responders had a duration of response >12 months.

In summary, the safety profile of naratuximab emtansine plus rituximab was tolerable and manageable, while demonstrating high efficacy. This treatment regimen could represent a new treatment option for patients with r/r DLBCL, including heavily pre-treated patients.

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2. Yair Levy M, et al. Safety and efficacy of CD37-targeting naratuximab emtansine plus rituximab in diffuse large B-cell lymphoma and other non-Hodgkin's B-cell lymphomas – a phase 2 study. P205-3, EHA 2021 Congress, 09–17 June.

Novel targets in myelofibrosis: overview of emergent therapies

Presented By

Prof. Francesco Passamonti, University of Insubria, Italy

Conference

EHA 2021

Several late-stage clinical trials show encouraging results for novel therapies for myelofibrosis in at least a subset of endpoints or patient populations. The novel agents, including pacritinib, momelotinib, parsaclisib, KRT-232, and tagraxofusp are directed at a variety of targets.

Prof. Francesco Passamonti (University of Insubria, Italy) gave an overview of the evolving therapeutic landscape of myelofibrosis (MF), which is moving beyond ruxolitinib alone [1]. Different pathways can be used to modify myelofibrosis: signal transduction inhibitors (e.g. JAK-inhibitors), apoptotic pathway enhancers, and agents harnessing host immunity [2].

The JAK2-inhibitor pacritinib was tested in phase 3 clinical studies (e.g. PERSIST-1 [**NCT01773187**]; PERSIST-2 [**NCT02055781**]) and shown to be effective in spleen volume response (SVR35) but not in total symptom score (TSS50) [3,4]. In a phase 2 study (**NCT04884191**), pacritinib was assessed as monotherapy in patients with ruxolitinib intolerance or resistance. Overall efficacy was poor, but in a subpopulation with severe thrombocytopaenia, SVR35 was 17% [5].

Momelotinib is another JAK-inhibitor being evaluated in phase 3 trials (SIMPLIFY-1 [**NCT01969838**]; SIMPLIFY-2 [**NCT02101268**]). Its efficacy was compared with ruxolitinib. SIMPLIFY-1 demonstrated robust overall survival (OS) for JAK-inhibitor-naïve patients (median OS ≥53.1 months). Momelotinib met the non-inferiority endpoint SVR35, but not TSS50. In SIMPLIFY-2, the JAK inhibitor also showed robust OS of a median 34.3–37.5 months. It failed to meet the primary endpoint for SVR35 but achieved the endpoint TSS50. Both studies showed a good safety profile [6,7].

A third signal transduction inhibitor is parsaclisib, a PI3K-inhibitor. In a phase 2 trial (**NCT04551053**), parsaclisib plus ruxolitinib was shown to be effective in SVR in patients with a suboptimal response to ruxolitinib. Haemoglobin level as well as platelet count were stable at 24 weeks [8].

Prof. Passamonti further presented results for KRT-232, an MDM2-inhibitor (apoptotic pathway enhancer), which is developed in the BOREAS phase 2 trial (**NCT03662126**) in patients with refractory or relapsing MF. The most effective dose showed SVR35 of 16% and a TSS50 of 30%. However, results may be confounded by a lack of ruxolitinib-washout [9].

CD123 could also be a useful target in MF patients with ruxolitinib failure. Tagraxofusp is a novel CD123-directed cytotoxic therapy developed in a phase 2 trial (**NCT02268253**). Results showed 56% spleen responses (by palpation at week 24), 46% symptom burden reduction, and 56% of patients were classified as having stable disease. The safety profile was considered good [10].

To conclude, the therapeutic landscape of MF is evolving. Many non-JAK inhibitor-based therapies are investigated in pre-clinical and early clinical studies and there are several novel therapies in late-stage clinical development. The future treatment landscape aiming to improve the lives of patients with MF looks encouraging.

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3. **Mesa RA, et al. Lancet Haematol 2017;4:e225-e236.**
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MAIA results confirm superior efficacy of daratumumab in combination with standard-of-care

Presented By

Prof. Thierry Facon, University of Lille, France

Conference

EHA 2021

Trial

Phase 3, MAIA

In patients with newly diagnosed multiple myeloma, daratumumab with standard-of-care (i.e. lenalidomide and dexamethasone) achieved superior outcomes in overall survival, progression-free survival, and overall response rate compared with standard of care alone, as demonstrated by the interim overall survival results of the phase 3 MAIA trial.

The phase 3 ALCYONE (**NCT02195479**), MAIA (**NCT02252172**), and CASSIOPEIA (**NCT02541383**) studies have previously established the progression-free survival (PFS) of daratumumab in combination with standard-of-care versus standard-of-care alone for patients with newly-diagnosed multiple myeloma (MM) [1-3]. ALCYONE also established, for the first time, an overall survival (OS) benefit of a daratumumab-based regimen in newly diagnosed MM [4]. In the previous MAIA update, OS data were not yet mature [5]. At the EHA 2021 congress, Prof. Thierry Facon (University of Lille, France) reported the updated efficacy and safety results from a pre-specified imterim analysis after a median follow-up of approximately 56 months [6].

Participants were randomised to receive daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone alone (Rd) until disease progression. The primary endpoint was PFS. Median duration of follow-up was 56.2 months, with 42% of patients in the D-Rd arm and 18% of patients in the Rd arm remaining on treatment. More patients discontinued for adverse events (AEs) in the Rd-arm than in the D-Rd arm. No new safety concerns were identified with longer follow-up.

The updated PFS data showed a 60-month PFS rate of 52.5% in D-Rd versus 28.7% in Rd. These data provide a new PFS benchmark in patients with newly diagnosed MM who are transplant ineligible. D-Rd also demonstrated a significant benefit in OS, with a 32% reduction in the risk of death: 60-month OS rate was 66.3% in D-Rd and 53.1% in Rd. A subgroup analysis confirmed OS benefit with D-Rd, as it was consistent across patient subgroups.

In summary, after almost 5 years of follow-up, a significant OS benefit of D-Rd versus Rd was demonstrated in patients with transplant-ineligible newly diagnosed MM, representing a 32% reduction in the risk of death. The significant benefit of D-Rd was maintained in PFS and no new safety concerns were identified with continuous therapy and longer follow-up. Prof. Facon concluded, "These results strongly support upfront D-Rd as new standard of care for patients with transplant-ineligible newly-diagnosed MM."

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4. **Mateos MV, et al. Lancet 2020;395(10218):132-141.**
5. **Kumar SK, et al. Blood;136(Suppl. 1):24-26.**
6. Facon T, et al. Overall survival results with daratumumab, lenalidomide, and dexamethase versus lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: phase 3 MAIA study. P205-1, EHA 2021 Congress, 09–17 June.

ELEVATE-RR: Acalabrutinib demonstrates similar efficacy and better safety compared with ibrutinib

Presented By

Prof. Peter Hillmen, St James's University Hospital, UK

Conference

EHA 2021

Trial

Phase 3, ELEVATE-RR

The phase 3 ELEVATE-RR trial was a head-to-head comparison of acalabrutinib versus ibrutinib in previously treated patients with chronic lymphocytic leukaemia. The first results of this study demonstrated that acalabrutinib had better tolerability than ibrutinib with fewer patients experiencing cardiovascular toxicities. Moreover, acalabrutinib had similar efficacy to ibrutinib concerning progression-free survival.

Bruton's tyrosine kinase (BTK) plays a critical role in chronic lymphocytic leukaemia (CLL) tumour cell migration, adhesion, proliferation, and survival. Ibrutinib was the 1st irreversible BTK inhibitor but is associated with adverse events (AEs), particularly cardiovascular toxicities, that can lead to treatment discontinuation. Acalabrutinib is a next-generation, more selective BTK inhibitor.

Prof. Peter Hillmen (St James's University Hospital, UK) reported the first results of the head-to-head phase 3 trial ELEVATE-RR (**NCT02477696**), which compared safety and efficacy of ibrutinib and acalabrutinib in patients with previously treated CLL and presence of del(17p) or del(11q) [1]. Patients were randomised 1:1 into 2 treatment arms and received either 100 mg acalubritinib twice daily or 420 mg ibrutinib once daily. The primary endpoint was non-inferiority on progression-free survival (PFS), which was then followed by superiority analysis in secondary endpoints of safety and efficacy.

Included were 533 patients, 268 received acalabrutinib and 265 received ibrutinib. The median duration of follow up was 40.9 months. More than half of the patients discontinued treatment, mainly due to disease progression, which was to be expected given that the patients were pre-treated. Median PFS was 38.4% in both arms. Thus, the primary endpoint, non-inferiority of PFS with acalabrutinib versus ibrutinib, was met.

First results of secondary endpoints were also presented: the incidence of any-grade atrial fibrillation/flutter was significantly lower with acalabrutinib, the incidence of grade ≥3 infection was similar between treatment arms, the incidence of Richter's transformation was similar, and the hazard ratio of overall survival was comparable. Summarising safety data revealed fewer AEs leading to treatment discontinuation and fewer deaths due to AEs for acalabrutinib, while any-grade and grade ≥3 AE incidences were comparable.

Prof. Hillmen concluded, "Acalabrutinib was non-inferior to ibrutinib in the primary endpoint PFS and demonstrated lower frequencies of common AEs. These results demonstrate that acalabrutinib is better tolerated and has similar efficacy to ibrutinib in patients with previously treated CLL."

1. Hillmen P et al. First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukaemia. P409-1, EHA 2021 Congress, 09–17 June.

GLOW: Ibrutinib plus venetoclax showed superior efficacy as first-line treatment of CLL

Presented By

Prof. Arnon Kater, Amsterdam University Medical Centre, the Netherlands

Conference

EHA 2021

Trial

Phase 3, GLOW

Fixed-duration ibrutinib plus venetoclax was a superior treatment in older or unfit patients with chronic lymphocytic leukaemia compared with chlorambucil plus obinutuzumab. These data support the positive clinical profile of all-oral, once-daily, fixed-duration ibrutinib plus venetoclax as first-line treatment for this patient population. These were the primary endpoint results of the phase 3 GLOW study.

Prof. Arnon Kater (Amsterdam University Medical Centre, the Netherlands) presented the primary results of the first phase 3 study (GLOW trial, **NCT03462719**) of fixed-duration ibrutinib plus venetoclax treatment in older or unfit adults with previously untreated chronic lymphocytic leukaemia (CLL) [1]. Ibrutinib plus venetoclax is a once-daily, all-oral, fixed-duration therapy inducing deep remissions in young or fit patients that demonstrated 2-year progression-free survival (PFS) of 95% in the phase 2 CAPTIVATE study (**NCT02910583**) [2].

A total of 211 patients ≥65 years of age or unfit patients aged <65 years with cumulative illness rating scales score (CIRS) >6 or creatinine clearance (CrCL) <70 mL/min were randomised 1:1 to receive ibrutinib plus venetoclax or chlorambucil plus obinutuzumab. The primary endpoint was PFS, key secondary endpoints included undetectable minimal residual disease (uMRD), complete and overall response rate, overall survival (OS), and safety.

With a median follow-up of 27.7 months, PFS for ibrutinib plus venetoclax was superior to chlorambucil plus obinutuzumab; ibrutinib plus venetoclax reduced the risk of progression or death by 78%. Median PFS was not reached with ibrutinib plus venetoclax, while median PFS was 21.0 months with chlorambucil plus obinutuzumab. The PFS analysis in pre-specified subgroups consistently favoured ibrutinib plus venetoclax. Complete response rates were significantly higher and more durable for ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab. The same was true for uMRD rate. The risk of needing second-line therapy was reduced by 86% with first-line ibrutinib plus venetoclax.

There were 11 deaths in the ibrutinib plus venetoclax arm and 12 in the chlorambucil plus obinutuzumab arm. Causes of death were similar in nature, with infections and cardiac events being most common. Median exposure was 13.8 months with ibrutinib plus venetoclax and 5.1 months with chlorambucil plus obinutuzumab. Interim safety results demonstrated serious adverse events in ≥5% of patients. Two patients discontinued ibrutinib due to atrial fibrillation.

In summary, fixed-duration ibrutinib plus venetoclax as first-line treatment for older or unfit adults with CLL demonstrated superior efficacy. Tolerability profiles were consistent with CLL treatment in elderly comorbid patients. Prof. Kater concluded, "The results of the phase 3 GLOW study support the positive clinical profile of all-oral, once-daily, fixed-duration I+V as first-line treatment for older patients with CLL."

1. Kater A et al. Fixed duration ibrutinib and venetoclax (I+V) versus chlorambucil plus obinutuzumab (Clb+O) for first-line (1L) chronic lymphocytic leukemia (CLL): primary analysis of the phase 3 GLOW study. P205-2, EHA 2021 Congress, 09–17 June.
2. **Ghia P et al. ASCO 2021: Abstract 7501.**

Fixed 12 cycles and MRD-guided venetoclax consolidation is highly effective in CLL

Presented By

Dr Mark-David Levin, Albert Schweitzer Hospital, the Netherlands

Conference

EHA 2021

Trial

Phase 2, HOVON 139/GiVe

Primary endpoint results of the phase 2 HOVON 139/GiVe trial demonstrate high efficacy and good tolerability after fixed 12 cycles of venetoclax or minimal residual disease-guided treatment with venetoclax after pre-induction with obinutuzumab. These results warrant further study of both these treatment options for patients with naïve chronic lymphocytic leukaemia who were unfit for first-line fludarabine, cyclophosphamide, and rituximab.

Fixed duration treatment of chronic lymphocytic leukaemia (CLL) patients with venetoclax combined with an anti-CD20 antibody results in high rates of undetectable minimal residual disease (uMRD) and prolonged progression-free survival (PFS) [1]. The next step in CLL treatment may be a tailored approach based on remission status.

The randomised, phase 2 HOVON 139/GiVe trial included naïve CLL patients that were unfit for first-line fludarabine, cyclophosphamide, and rituximab and studied the impact of a standard or MRD-based addition of venetoclax for 12 cycles after induction treatment with obinutuzumab plus venetoclax. Dr Mark-David Levin (Albert Schweitzer Hospital, the Netherlands) presented the primary endpoint analysis after a maximum of 24 cycles [2].

Patients (n=70) received 2 cycles of obinutuzumab for pre-induction followed by induction with 6 cycles of obinutuzumab plus venetoclax, subsequently followed by 6 cycles of venetoclax monotherapy. Patients were thereafter randomised 1:1 to maintenance therapy in 2 arms. Arm A received venetoclax for 12 additional cycles irrespective of MRD status and arm B received MRD-guided venetoclax. After obinutuzumab pre-induction treatment, the risk of tumour lysis syndrome (TLS) was downgraded in a majority of patients. At randomisation, uMRD was 79% to 88%.

After obinutuzumab pre-induction overall response rate (ORR) was 43%, which increased after the venetoclax monotherapy to 97%. The primary endpoint was the proportion of patients who had MRD-negative bone marrow after a maximum of 24 cycles of venetoclax and no progression at any earlier time point after randomisation. In arm A (n=32), 28 patients received 12 cycles of venetoclax; 19 patients showed uMRD and no progression. In arm B, patients who were MRD-negative at randomisation did not start venetoclax treatment. In arm B (n=30), only 1 patient received 3 cycles of venetoclax; 17 patients showed uMRD and no progression. The safety profile of arms A and B were similar with some advantages in arm B. Adverse events were mostly pulmonary infections.

In summary, 2 cycles of obinutuzumab pre-induction abrogated TLS risk in a large majority of patients receiving obinutuzumab plus venetoclax. Venetoclax consolidation treatment, both at fixed cycles and MRD-based, was highly effective and well tolerated.

1. **Kater AP et al. J Clin Oncol 2020;38(34):4042-54.**
2. Levin MD et al. MRD-guided or fixed 12 cycles of venetoclax consolidation after venetoclax plus obinutuzumab treatment in first-line FCR-unfit patients with CLL: primary endpoint analysis of the HOVON 139/GiVe trial. P409-5, EHA 2021 Congress, 09–17 June.

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Final analysis of the EURO-SKI study: primary endpoints met in chronic myeloid leukaemia

Presented By

Prof. Susanne Saußele, Heidelberg University, Germany

Conference

EHA 2021

Trial

EURO-SKI

3-Year results of the EURO-SKI showed that approximately half of the patients with chronic myeloid leukaemia were in treatment-free remission. EURO-SKI evaluated the duration of treatment-free molecular response and survival after cessation of treatment with tyrosine kinase inhibitors in patients with chronic myeloid leukaemia.

Treatment cessation has become a realistic therapy goal since the introduction of tyrosine kinase inhibtors (TKIs) for the treatment of chronic myeloid leukaemia (CML), with treatment-free remission being achievable in up to 55% of patients with deep molecular response. However, little is known about prognostic indicators of sustained treatment-free remission. Thus, the EURO-SKI study (**NCT01596114)** was designed to define prognostic markers to increase the rate of patients in durable deep molecular response after TKI treatment cessation. Prof. Susanne Saußele (Heidelberg University, Germany) presented the final analysis after 3-years follow-up [1].

The study enrolled 728 participants with chronic CML, who were on TKI treatment and in confirmed deep molecular response. Primary endpoints were molecular recurrence-free survival (MRecFS) at 6 and 36 months. Patients were followed for 3 years after cessation of TKI treatment [2].

The final result at 36 months was 48% for MRecFS and 46% for molecular treatment-free survival, as 15 patients re-started TKI therapy without major molecular response (MMR) loss. Respective data for 6 months were 62% and 61%; and for 12 months it was 55% and 54%, respectively. The cumulative incidence of MMR loss was 50% at 36 months. Nine deaths occurred that were not correlated with MMR relapse, CML or trial design.

The first primary endpoint, MRecFS at 6 months, was met: 434 out of 713 patients (61%) were in MMR or better. The null hypothesis of MMR maintenance at 6 months ≤40% was rejected. Also the secondary primary endpoint, MRecFS at 36 months, was met: 309 out of 678 patients (46%) are still in MMR or better. The null hypothesis of MMR maintenance at 36 months ≤35% was rejected.

In summary, the primary endpoints of the EURO-SKI study were met and MRecFS probabilities were 62% and 46% after 6 and 36 months. respectively. First prognostic analyses support the importance of TKI treatment duration for MMR loss, with further prognostic analyses to follow. The EURO-SKI study outlines important preconditions that can be employed as guidance for stopping criteria.

1. Saußele S, et al. Final analysis of a pan European stop tyrosine kinase inhibitor trial in chronic myeloid leukemia: the EURO-SKI study. S152 EHA 2021 Congress, 09–17 June.
2. **Saußele S, et al. Lancet Oncol 2018;19(6):747-757.**

ELEVATE-TN 4-year follow-up: acalabrutinib shows superior efficacy in chronic lymphocytic leukaemia

Presented By

Dr Jeff Sharman, US Oncology Network, USA

Conference

EHA 2021

Trial

ELEVATE-TN

Acalabrutinib with or without obinutuzumab demonstrated superior efficacy over obinutuzumab + chlorambucil in patients with chronic lymphocytic leukaemia. Results from the 4-year follow-up of the ELEVATE-TN study confirmed previously shown interim results.

Bruton's tyrosine kinase (BTK) plays a critical role in chronic lymphocytic leukaemia (CLL) tumour cell migration, adhesion, proliferation, and survival. Acalabrutinib is a next-generation, potent, highly selective BTK inhibitor.

Dr Jeff Sharman (US Oncology Network, USA) discussed 4-year follow-up results of the multicentre, open-label, phase 3 ELEVATE-TN study (**NCT02475681**) [1], which was designed to compare efficacy and safety of acalabrutinib (A) ± obinutuzumab (O) versus obinutuzumab + chlorambucil (Clb) in patients with treatment-naïve chronic lymphocytic leukemia (CLL). Previously reported interim results demonstrated superior efficacy and acceptable tolerability of acalabrutinib ± obinutuzumab [2].

Patients (n=535) with previously untreated CLL with comorbidities were randomised into 3 treatment arms: acalabrutinib + obinutuzumab (n=179), acalabrutinib monotherapy (n=179), and obinutuzumab + chlorambucil (n=177), with similar patient characteristics at baseline. Crossover from obinutuzumab + chlorambucil to acalabrutinib was allowed after progression. The primary efficacy endpoint was progress-free survival (PFS).

Median follow-up was 46.9 months. PFS was significantly prolonged in patients receiving acalabrutinib + obinutuzumab versus obinutuzumab + chlorambucil treatment, in acalabrutinib monotherapy versus obinutuzumab + chlorambucil , and in acalabrutinib + obinutuzumab versus acalabrutinib monotherapy. Median PFS was not reached in treatment arms acalabrutinib + obinutuzumab and acalabrutinib monotherapy, median PFS was 27.8 months with obinutuzumab + chlorambucil. The 48-month PFS rate was 87% for acalabrutinib + obinutuzumab, 78% for acalabrutinib monotherapy, and 25% for obinutuzumab + chlorambucil .

Median overall survival was not reached in any treatment arm. At 48 months, overall survival rates were 93%, 88%, and 88%, which was not statistically significantly different. At 60 months, there were still notably fewer deaths with acalabrutinib + obinutuzumab compared with other treatment arms.

More than 25% of patients in any treatment group experienced adverse events, as already reported in the interim analysis [2]. Most of the adverse events occurred in the first year of treatment and declined over time. No new safety signals were observed.

Dr Sharman concluded, "acalabrutinib with or without obinutuzumab demonstrates durable disease control, tolerability, and flexibility to tailor treatment as a monotherapy or combination therapy in treatment-naïve CLL patients."

1. In Sharman JP, et al. Acalabrutinib ± obinutuzumab vs. obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: ELEVATE-TN 4-year follow-up. P409-4, EHA 2021 Congress, 09–17 June.
2. **Sharman JP, et al. Lancet 2020;395:1278-91.**

Gene therapy: A promising approach for hereditary haemoglobinopathies

Presented By

Dr Haydar Frangoul , Sarah Cannon Research Institute, USA

Conference

EHA 2021

Gene addition and gene editing approaches for sickle cell disease and transfusion-dependent β-thalassemia show encouraging results in clinical studies. Long-term follow-up will be required to assess the long-term safety and durability of gene expression [1].

Sickle cell disease affects 270,000 infants born yearly worldwide, leading to chronic hemolysis and vaso-occlusive crises (VOCs) [2]. β-thalassemia affects 40,000 infants born each year, approximately half of them being transfusion-dependent. Patients suffer from iron overload, thrombosis, skeletal, and cardiopulmonary symptoms. Allogeneic stem cell or bone marrow transplant from HLA-identical donors are the only available curative treatments so far. Dr Haydar Frangoul (Sarah Cannon Research Institute, USA) presented gene therapy approaches for 2 hemoglobinopathies caused by mutations: sickle cell disease and transfusion-dependent β-thalassemia (TDT) [1].

There are 2 approaches to gene therapy: gene editing and gene addition. An example of a gene-addition approach in haemoglobinopathies is a lentiviral vector encoding a modified β-globin gene including an anti-sickling mutation. In a phase 1/2 study including 32 patients with sickle cell disease (**NCT02140554**), LentiGlobin treatment was shown to effectively prevent vaso-occlusive crises [3].

Dr Frangoul also presented a gene-editing approach to increase foetal haemoglobin (HbF) production. In sickle cell disease and TDT symptoms occur when haemoglobin is switched from foetal to adult, while in patients with persistent HbF, less or no symptoms are present. A CRISPR-Cas9 gene-editing tool (CTX001) was used to increase the expression of HbF [4]. Patients were infused with CTX001 and followed up for Hb production, HbF expression, transfusion requirements (TDT; **NCT03655678**) and VOCs (sickle cell disease; **NCT03745287**).

Preliminary results of 7 TDT-patients (median follow-up 8.9 months) showed a clinically meaningful expression of HbF and increased total haemoglobin (Hb) were achieved and maintained, and all patients became transfusion independent. CTX001 was also used in sickle cell disease patients and the first results were presented at the EHA 2021 Congress (n=3; median follow-up 7.8 months). Foetal Hb represented 31–47% of total Hb after 3 months with an increase at later time points. A pancellular HbF expression of almost 100% was seen. All patients were VOC-free [5].

Despite encouraging results, gene therapy approaches still have limitations. Recently reported cases of myelodysplastic syndrome and acute myeloid leukemia after receiving LentiGlobin (**NCT02140554**, **NCT04293185**) underscore the need for long-term safety data.

Dr Frangoul concluded that "gene therapy approaches can offer an alternative to allogeneic stem cell transplant especially for patients who lack an HLA-identical donor". Data for gene addition and gene editing approaches are promising. Additional follow-up is required to determine the long-term safety and persistence of gene-modified cells in the marrow.

1. Frangoul H. Gene therapy approaches to treatment of hemoglobinopathies. P210-1, EHA 2021 Congress, 09–17 June.
2. **DeBaun MR, et al. Blood 2019;133(6):615–617**
3. **Thompson A. Abstract 365, ASH 2020, 05–08 December.**
4. **Frangoul H, et al. N Engl J Med 2021;384(3):252–260.**
5. Grupp S, et al. EP736, EHA 2021 Congress, 09–17 June.

BEYOND study: Luspatercept improves anaemia in patients with non-transfusion-dependent β-thalassaemia

Presented By

Prof. Ali Taher, American University of Beirut Medical Center, Lebanon

Conference

EHA 2021

Trial

Phase 2, BEYOND

Results from the phase 2 BEYOND study demonstrated the safety and efficacy of luspatercept in patients with non-transfusion-dependent β-thalassaemia. A durable increase in haemoglobin levels was achieved, which was associated with increased quality of life scores.

Beta-thalassemia is an inherited haemoglobinopathy characterised by impaired haemoglobin (Hb) production, chronic anaemia, and iron overload, affecting survival and quality of life. Tailored red blood cell transfusions and novel therapies target key pathophysiologic mechanisms in transfusion-dependent β-thalassaemia (TDT) and non-TDT. Patients with non-TDT do not require lifelong regular transfusion for survival; however, they may require occasional transfusions during pregnancy, surgery, or infection [1]. The Hb level significantly correlates with morbidity-free survival in non-TDT: increase of Hb from Hb <8 to >10 g/dL in steps of 1 g/dL dramatically decrease odds of developing morbidities [2]. This underscores the need for effective management options for anaemia in non-TDT. Thus, the phase 2, multicentre, double-blind, placebo-controlled BEYOND study (**NCT03342404**) aimed to evaluate the safety and efficacy of luspatercept, which has been approved for the treatment of anaemia in adult patients with TDT, in the treatment on non-TDT. Participants (n=145) were randomised in a 2:1 ratio to double-blinded treatment with luspatercept or placebo. The primary endpoint was ≥1.0 g/dL mean Hb increase from baseline.

Prof. Ali Taher (American University of Beirut Medical Center, Lebanon) presented the results. The study met its primary endpoint: 77.1% of patients in the luspatercept arm versus 0% in the placebo arm achieved a mean Hb increase of ≥1.0 g/dL from baseline. A key secondary endpoint was improvement in quality of life as assessed in NTDT-PRO T/W scores from baseline. An improvement occurred more frequently in patients receiving luspatercept and was consistently improving through week 78. The improvement in NTDT-PRO T/W score was significantly correlated with Hb increase. The safety profile of luspatercept was favourable: no deaths, malignancies, or thromboembolic events were reported.

Prof. Taher summarised, "Clinical benefit of luspatercept treatment, previously observed in patients with TDT through a significant reduction in red blood cell transfusion burden, has now also been observed in patients with non-TDT, as measured by meaningful improvement of anaemia."

1. Taher AT, et al. The BEYOND study: results of a phase 2, double-blind, randomized, placebo-controlled multicenter study of luspatercept in adult patients with non-transfusion dependent beta-thalassemia. P204-2, EHA 2021 Congress, 09–17 June.
2. **Musallam KM, et al. Ann Hematol 2021; 20 Jan. DOI:10.1007/s00277-020-04370-2** .