Abstract Highlights

Classical Hodgkin lymphoma, acute promyelocytic leukaemia, post-transplant relapse, massive transfusion, and many more essential topics in haematology were explored in several unique and insightful abstracts presented at the European Hematology Association (EHA) 2023 Congress.

Citation: EMJ Hematol. 2023;11[1]:41-47.
DOI/10.33590/emjhematol/10305989.
https://doi.org/10.33590/emjhematol/10305989.

Is There a Correlation Between Progression-Free and Overall Survival in Classical Hodgkin Lymphoma?

PROGRESSION-FREE survival (PFS) is often a primary endpoint in clinical trials as a measurement of treatment efficacy. Another of these treatment efficacy measures is overall survival (OS). Despite this, the relationship between PFS and OS is unknown.

Researchers from the German Hodgkin Study Group evaluated whether there is a correlation between PFS and OS following first-line treatment for patients with classical Hodgkin lymphoma (HL). The team analysed data obtained during and after polychemotherapy from 10,605 patients with classical HL, who were enrolled across nine Phase III randomised German Hodgkin Study Group first-line clinical trials between January 1993–August 2018. PFS and OS were defined as time from randomisation until progression, relapse, or death, and time from randomisation until death, respectively.

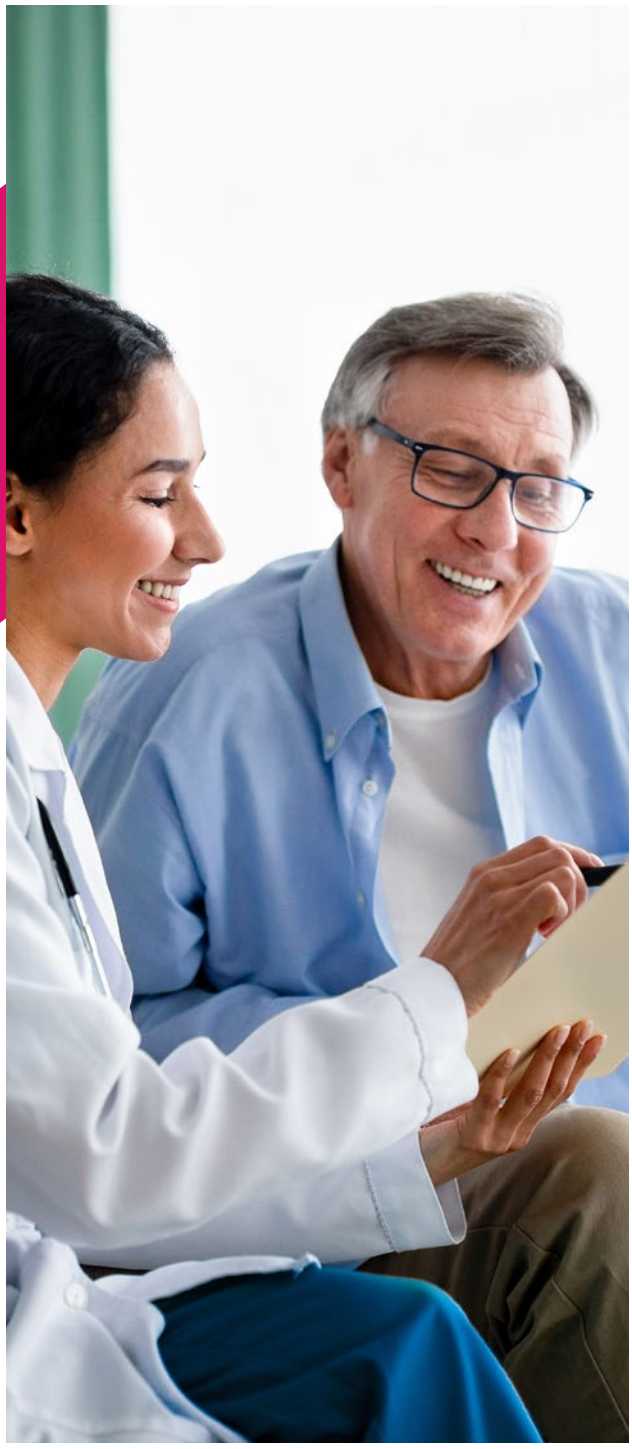
Records of ≥1 PFS and ≥1 OS event occurred for 1,682 and 1,064 patients, respectively. A significant and high correlation was seen at the trial level for treatment effects on PFS and OS (Pearson correlation coefficient [Pearson r]: 0.72; r^2=0.54; p<0.001). Application of a multiple regression model to account for differing effectiveness of experimental treatments and historical progress over trial generation yielded an r^2 of 0.93. In addition to this, analysis at the patient level also showed a high correlation between PFS and OS.

For the clinical trials, the researchers found that the average Pearson r was 0.74 (range: 0.61–0.85), with p<0.001 for each trial. All bar two trials showed high correlation, with Pearson r values of >0.70. Furthermore, Pearson r was higher in more advanced stages of HL. At the patient level, a high correlation was noted between the effects of risk factors on PFS and OS (Pearson r: 0.74–0.85; each p<0.001 using Wei–Lin–Weissfeld method to apply marginal Cox PH models for multiple endpoints) and PFS and OS directly (Pearson r: 0.72–0.83; each p<0.001 using copula models), were also identified.

> **"Analysis at the patient level also showed a high correlation between PFS and OS."**

The researchers concluded that PFS can predict treatment effects on OS in advance of reliable OS evaluation, as there is a high correlation between PFS and OS, as well as treatment effects and prognostic effects of risk factors on PFS and OS in first-line clinical trials in classical HL. ●

Factors Associated with Long-Term Survival in a Patient Cohort with Acute Promyelocytic Leukaemia



"The HARMONY registry includes 1,868 patients with APL diagnosed between 2007–2020."

Acute promyelocytic leukaemia (APL) is currently curable in 75–90% of patients using targeted agents, such all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), or ATRA combined with chemotherapy (ATRA+idarubicin, AIDA-based). The HARMONY registry enabled the merging of APL patient populations from both clinical trials and real-world settings, aiming to address unresolved aspects in the management of the disease. The HARMONY registry includes 1,868 patients with APL diagnosed between 2007–2020.

At the EHA Congress 2023, held in Frankfurt, Germany, Maria Teresa Vosso, Tor Vergata University of Rome, Italy, presented data from the HARMONY registry, which analysed factors associated with long-term survival in patients with APL.

Vosso and colleagues analysed patients (n=674) who underwent treatment and met the data quality requirements. Of these, 320 patients were treated with ATRA-ATO (median age: 48.5 years; range: 16–87; 47.8% female), while the remaining 354 were treated with AIDA (median age: 47.0 years; range: 17–82; 51.1% female). The data were harmonised and transformed using an Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM), and ultimately registered in the HARMONY Big Data platform.

The results revealed that patients treated with the ATRA-ATO regimen had a 92% overall survival rate at the 10-year mark, whereas those treated with the AIDA regimen had an 85% survival rate. The survival advantage was consistent across various risk groups, as determined by the Sanz risk-score. Additionally, age emerged as a crucial factor, with younger patients exhibiting better outcomes.

Based on a large international patient cohort, these findings affirm the significant survival benefit of the ATRA-ATO chemotherapy-free regimen for patients with APL, irrespective of their risk profile. ●

Chimeric Antigen Receptor T Cell Therapy for Post-Transplant Relapse

RESULTS from a retrospective study assessing outcomes following chimeric antigen receptor (CAR) T cell therapy, tisagenlecleucel (Tisa-cel), for post-haematopoietic stem cell transplant (HSCT) relapse in young patients (≤25 years) with CD19 positive acute lymphoblastic leukaemia (ALL), were presented at the EHA Congress 2023.

Data from 145 consecutive patients at 27 centres across seven European countries, who received Tisa-cel as treatment for post-HSCT relapse between 1st September 2018–1st January 2022, were evaluated. Median patient age was 9 years (range: 1–25 years). Of the 145 patients, 71 (57%) had <5% leukaemic blasts in their bone marrow upon lymphodepleting chemotherapy, 53 (43%) had >5% leukaemic blasts, and data was missing for 21 patients. Post-HSCT relapse occurred in ≤6 months for 38 patients (30%) and >6 months in 87 patients (70%). Those who relapsed at >6 months were deemed late relapsed patients, and those who relapsed within 6 months were deemed early relapsed.

The study found that 2-year event-free survival (EFS) and 2-year overall survival (OS) was 44.3% (±4.8%) and 64.0% (±4.7%), respectively. At Day 28, 135 of the total 145 patients were in remission; of these, the 2-year relapse-free survival was 46.1% (±5.1%); the 2-year non-relapse mortality was 1.6% (±1.1%); and the 2-year probability of persistent B cell aplasia was 46.3% (±6.7%).

For early relapsed patients, 2-year EFS was 19.5% (±8.3%) compared to 53.0% (±6.3%) for late relapsed patients (p=0.001). The 2-year OS was 35.9% (±9.2%) and 78.2% (±5.3%) for early and late relapsed patients, respectively (p<0.001). Alongside improved 2-year EFS and 2-year OS, 2-year relapse-free survival was also higher in late relapsed patients, at 51.9% (±6.6%) compared to 24.0% (±10.0%) for early relapsed patients (p=0.020).

"Alongside improved 2-year EFS and 2-year OS, 2-year relapse-free survival was also higher in late relapsed patients."

The 2-year cumulative incidence of relapse after Tisa-cel was lower in late relapsed patients than early relapsed patients at 42.8% compared to 70.4% (p=0.006). The 2-year persistent B cell aplasia was higher in late relapsed patients than early relapsed patients (55.5% and 13.7%, respectively), which could be suggestive of CAR-T cell sub-potency in patients who experience early relapse. Cytokine release syndrome occurred in 79 patients (63%), and immune effector cell-associated neurotoxicity syndrome occurred in 13 patients (11%).

The authors concluded that late relapsed patients treated with a single Tisa-cel infusion and no further consolidation have an excellent prognosis, and that T cell effector function may be sub-potent, resulting in early CAR-T cell loss in early relapsed patients. ●

Sex Differences in Patients with Sickle Cell Disease

SICKLE cell disease (SCD) is a disorder with a range of clinical manifestations. This variability is determined by several factors, including biological sex. The King's College Hospital, London, UK, patient record system was therefore used to examine a cohort of homozygous patients with SCD (HbSS) and heterozygous patients with SCD (HbSC). The effects of sex on a range of laboratory measurements and clinical parameters were investigated, with the aim of extending understanding of sex differences in SCD outcomes.

A total of 802 individuals with HbSS (median age: 35.1 years; 54% female) and 267 with HbSC (median age: 45 years; 64% female) were included in the study. Analysis of variance was used to test the association between sex and clinical laboratory measurements.

Data suggested male sex was associated with increased haemoglobin, absolute reticulocyte count, and haematocrit in individuals with HbSS and HbSC. Males with HbSS also had increased inflammatory markers compared to females, with elevated eosinophils (p=0.00043), monocytes (p=3.9E-08), and C-reactive protein (p=4.4E-06). Liver function test and estimated glomerular filtration rate were increased in males with HbSS, but not HbSC.

For patients receiving hydroxyurea therapy, unpaired T-tests were utilised to compare responses based on sex. The increase in foetal haemoglobin, total haemoglobin, and mean corpuscular volume during hydroxyurea treatment was significantly higher in females than males (p=0.00098, p=0.046, p=0.012, respectively).

Further analysis showed that males also had a higher incidence of all adverse cerebrovascular outcomes, and males with HbSS demonstrated an increase in the number of hospitalisations per year (p=0.04) compared to females. However, survival analysis of nearly 900 patients showed that sex had no effect on survival in individuals with HbSS and HbSC (p=0.77), with median survival of 62 and 80 years, respectively.

Overall, males with HbSS had worse disease outcomes across almost all SCD aspects when compared to females. However, males did have higher haemoglobin, usually associated with a milder phenotype, and a difference in survival was not identified. Increased understanding of how sex affects the pathophysiology of SCD will ultimately lead to improved clinical management, and thus warrants further investigation.

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Has a Definition for Massive Transfusion Been Found?

RESEARCH into the definition of massive transfusion (MT), which indicates there is significant heterogeneity in the current definitions used in randomised controlled trials (RCT), was presented at EHA 2023. Currently, there is no standardised definition in use, making it difficult to compare efficacy and safety data across studies on patients who are critically bleeding.

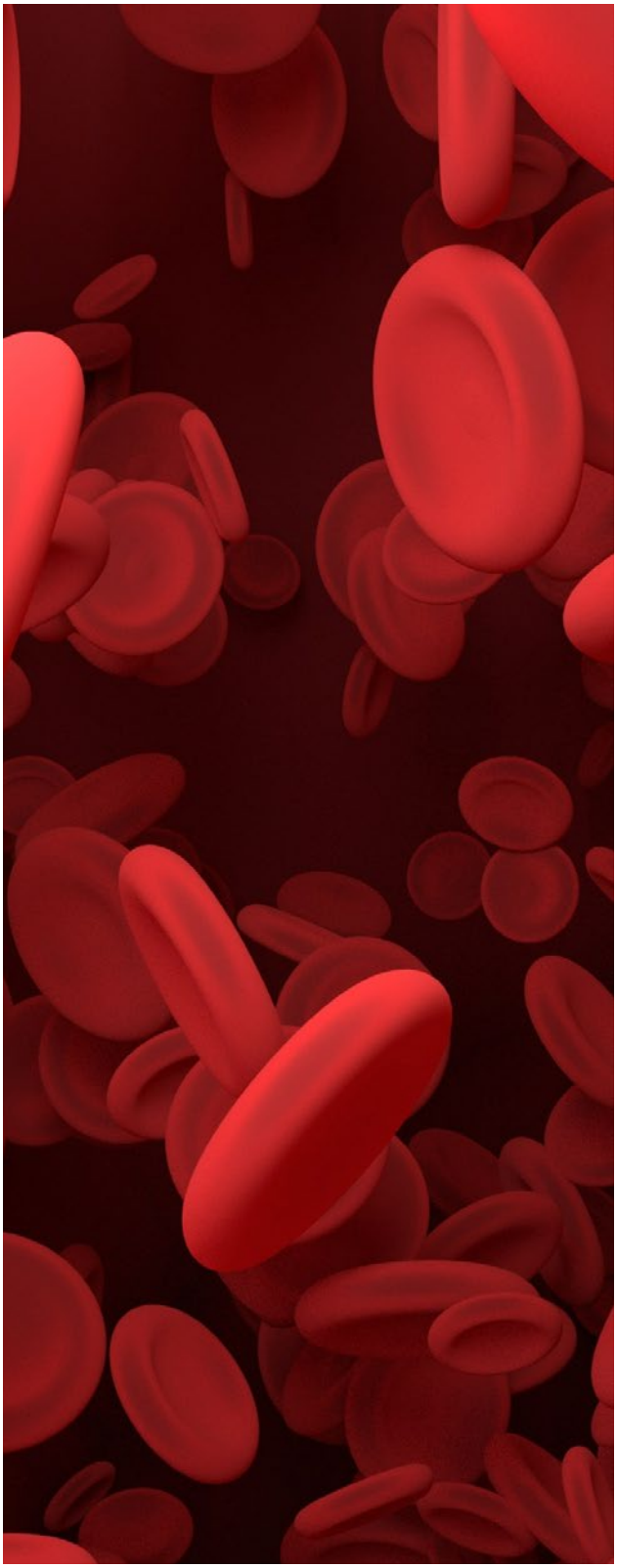
Victor Lin, Monash University, Melbourne, Australia, and colleagues, performed a scoping review of MT-related RCTs to evaluate currently used definitions. They searched for RCTs on numerous databases from inception until 11th August 2022. There was no language restriction, and trials could be ongoing.

In the initial search, a total of 8,460 distinct references were found. The inclusion criteria included being an RCT; having a specific definition of MT; and including adult patients with an acquired bleeding disorder who had received, or were to receive, an MT in a clinical setting. Content other than RCTs was excluded. Of the identified references, only 30 studies met the criteria.

The researchers noted a lack of uniformity in the definitions of MT, with 15 distinct definitions being used in RCTs across four different specialities. These included trauma and obstetrics/gynaecology, as well as orthopaedic and cardiothoracic surgery.

Most definitions were based on the number of red blood cell (RBC) units or whole blood administered within a certain time interval, while none included other blood products, such as plasma, and others did not specify the interval time. However, the researchers discovered that the most common definition was ≥10 RBC units in 24 hours, which appeared in 33% of the RCTs. This was preferred in trauma, featuring in 60% of RCTs, while obstetrics/gynaecology RCTs favoured >5 RBC units. In more recent studies, the trend was to use shorter timeframes.

With these findings, the researchers believe that a standardised definition of MT can be developed; one that will balance the strengths and weaknesses of previous definitions, and can be applied consistently in future RCTs.



"There is no standardised definition in use, making it difficult to compare efficacy and safety data."

Luspatercept in Patients with Non-Transfusion-Dependent β-Thalassaemia

UNTREATED anaemia in patients with non-transfusion-dependent β-thalassaemia (NTDT) can cause serious clinical complications. At the moment, there is no approved treatment for NTDT-associated anaemia; however, research has suggested that luspatercept could durably increase haemoglobin (Hb) levels and decrease transfusion burden in patients with NTDT. A study, presented at EHA 2023, looked into long-term efficacy data from patients in the BEYOND trial receiving luspatercept.

Participants were included in the study if they had NTDT or HbE/β-thalassaemia, defined as 0–5 red blood cells units transfused in the 24 weeks before randomisation, and Hb ≤10 g/dL. They were randomised to receive either placebo, or luspatercept 1.0–1.25 mg/kg subcutaneously for a duration of ≥48 weeks. Those receiving placebo were assessed up to discontinuation or crossover to luspatercept, while those receiving luspatercept were assessed on treatment. The team assessed mean change in Hb up to Week 144, in continuous 12-week intervals, as well as incidence of red blood cell transfusion events and units transfused. A mean change in Hb from baseline of ≥1 g/dL was defined as erythroid response.

Mean Hb change from baseline was 1.28 g/dL in Weeks 1–12, and 1.48 g/dL in Weeks 13–24 in the luspatercept arm. This increase was maintained in those remaining on study across all time points. The team noted nominally significant Hb level improvements from baseline up to Week 96 compared to placebo. In those taking luspatercept, mean change in liver iron content at Week 48 was 0.24 mg/g dry weight.

Furthermore, the team noted an increase in the proportion of patients with an erythroid response during any 12-week interval from 91.7% at the primary data cut-off date, to 93.8% at the current data cut-off date. There was also an increase in luspatercept arm responders, with ≥1 12-week rolling response from 35.2% to 61.1% between the cut-off dates, as well as an increase in mean total duration of erythroid response in patients with ≥1 12-week rolling responders from 611.1 to 873.1 days.

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The team noted a smaller proportion of transfusions in those receiving luspatercept compared to placebo (10.4% versus 32.7%), and lower mean number of units transfused and transfusion events in the luspatercept group compared to placebo. In those receiving luspatercept, mean number of units and events remained stable in Weeks 97–144.

The team concluded that in patients with NDT receiving long-term luspatercept, Hb levels were sustained and significantly improved, and erythroid response duration improved with an additional year of luspatercept. Cumulative incidence of transfusions stayed low and relatively stable throughout. ●