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Contents

Evolving CBC testing technology: Leveraging digital microscopy in blood diagnostics

Complete blood count (CBC) testing has historically occurred in central laboratories due to a lack of accurate point-of-care technology. Sight Diagnostics aims to change this paradigm with Sight OLO® — an AI-driven haematology analyser that produces CBC results with lab-grade precision in a fraction of the time at the point of care.

Support for the development of this article was provided by Sight Diagnostics

Since the inception of the Coulter Principle – automated CBC testing that harnesses resistive pulse sensing or flow cytometry to evaluate blood specimens – seven decades ago, reputable haematology systems have relied on large laboratory equipment that requires a special set-up for reagent management and liquid waste disposal. Although many of these robust systems are respected worldwide for their accuracy and speed, they have not suited point of care (POC) settings since they require high overheads and skilled lab technicians for daily quality control, calibration and maintenance.

For large clinical laboratories running countless CBC tests per day, these complex and expensive haematology systems – regardless of a delay in reporting results due to the transportation of specimens to central laboratories – are deemed cost-effective and efficient, but for small laboratories with small to medium test volumes or point of care settings with time-sensitive cases, this can be limiting or prohibitive. Hence there is an opportunity within the blood diagnostics industry to address these system inefficiencies and develop a system that enables faster, non-compromising, on-site CBC testing closer to patients without transporting specimens to one central laboratory.[1]

Challenging the Coulter Principle for POC settings

Over the years, there have been attempts to miniaturise legacy lab analysers, but due to the simplification of an often highly complex system, this miniaturisation has often resulted in "reduced numbers of parameters" (e.g., three-part instead of five-part differential), narrowed reportable ranges, reduced abnormal cell flagging capabilities and, in some cases, a reduction in accuracy (as indicated by the small number of FDA clearances). These CBC analysers have also inherited many of the product attributes of their larger relatives, including the requirements for liquid reagent replacement, washout and calibration procedures, and frequent quality-control processes," which in the point of care context can be very restrictive.[2]

Figure 1. Sight Diagnostics OLO self-contained haematology analyser

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Sight OLO represents a new breed of blood diagnostic technology

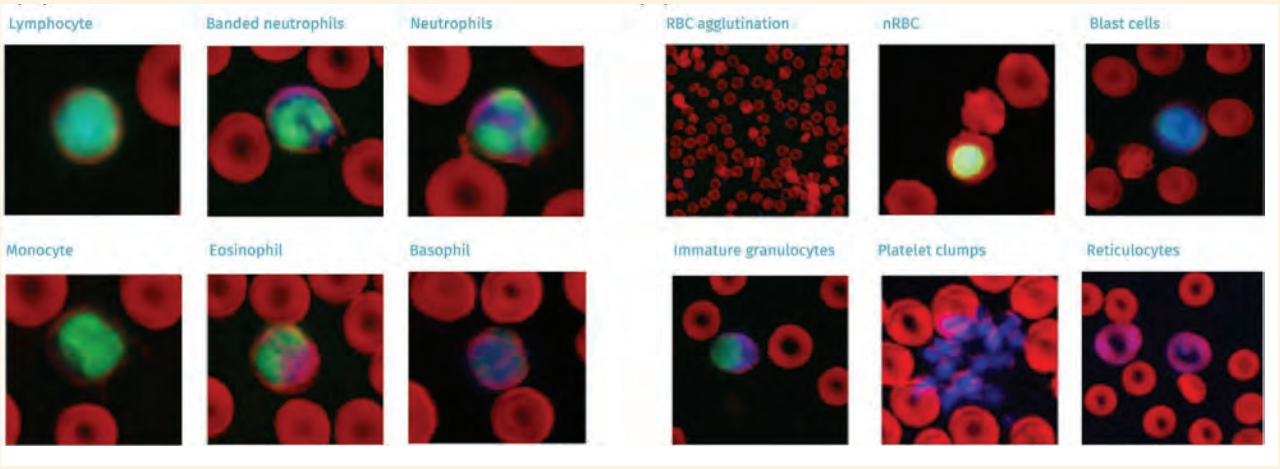
Developed from a decade of research, Sight OLO – an AI-driven haematology analyser – implements innovations in physics, chemistry, biology, optics, sample preparation and computer science to provide actionable five-part differential CBC results at the POC in minutes.

The self-contained quantitative multi-parameter analyser and its disposable cartridge deliver fast and accurate CBC results by digitising blood samples. According to Yossi Pollak, the co-founder and CEO of Sight Diagnostics, OLO takes two drops of blood and automatically creates a monolayer of cells within the self-contained cartridge. Once the specimen cartridge is placed inside the analyser, the device captures over 1000 images within minutes. Then – in real-time – the device uses artificial intelligence to classify, enumerate and identify anomalies in the blood samples to produce the final CBC results.[1]

Building on OLO's excellent performance, Sight constantly evolves OLO's AI-powered CBC models as well as exploring ways to expand on the application of OLO's underlying technology. For example, machine vision-based technology enables the digitalisation of blood samples into image data. This image data continues to fuel further research and development efforts into clinical conditions with visual signatures in the blood samples.

FIGURE 2

The Sight OLO haematology analyser. (D,E) False-coloured micrographs collected using OLO's multispectral microscopy. Red channel: haemoglobin absorption; green channel: nuclear DNA fluorescence; blue channel: cytoplasmic staining. (D) Characteristic examples of different white blood cell types. (E) Characteristic examples of different anomalous cell types and formations. *From AJH 2021;96(10):1266.*



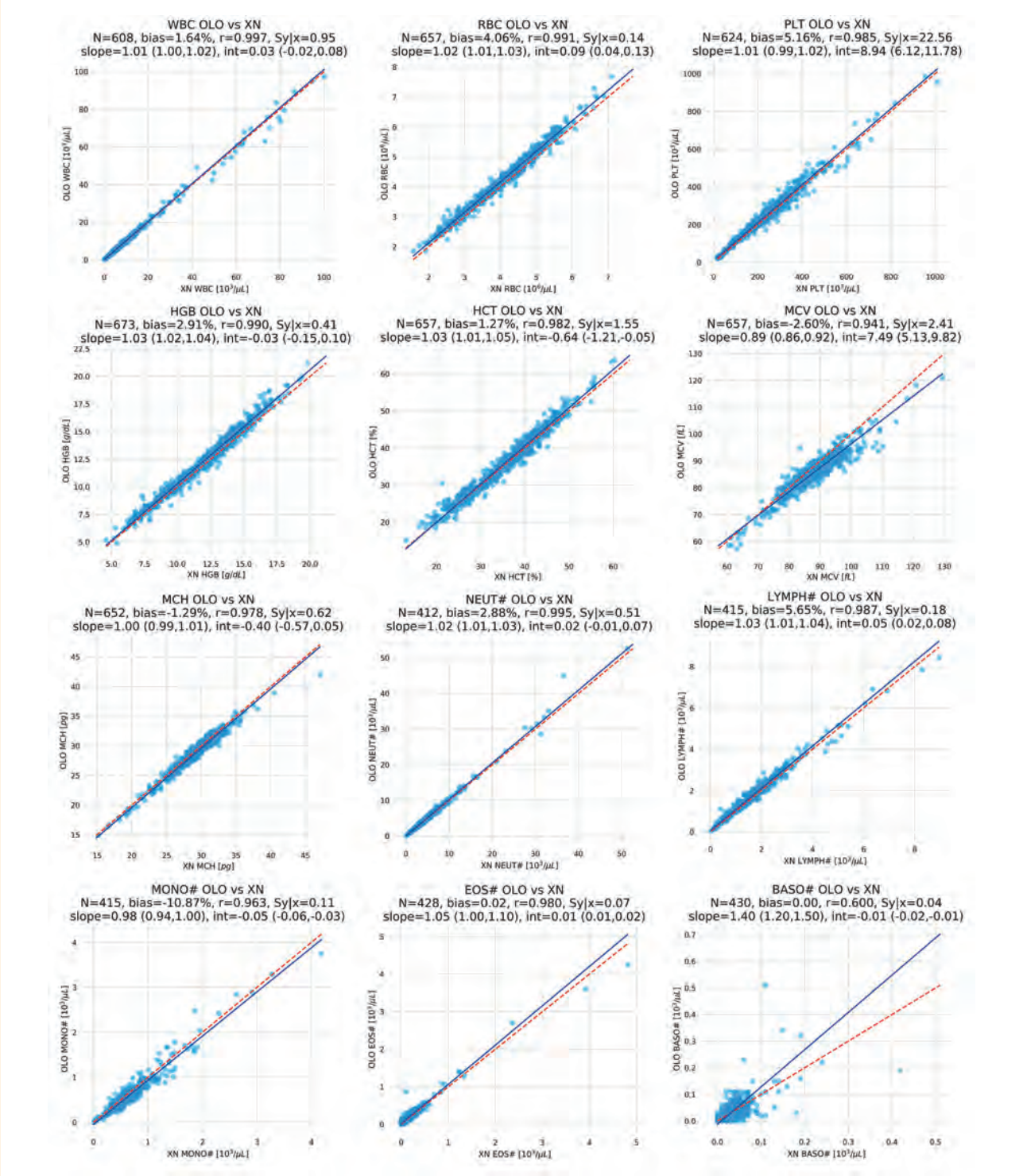
> OLO's performance is comparable to analysers that are 50-times bigger and much more complicated to operate. The ability to take that much analytical power outside of the central lab and bring it to any setting where you can perform a CBC analysis in minutes has huge implications for hospital wards, such as oncology clinics, emergency rooms and beyond.
>
> Dr Carlo Brugnara, Director of the Haematology Lab at the Boston Children's Hospital in Boston, Massachusetts, US.

Lab-grade accuracy for all CBC parameters at the POC

During a Sight study published in July 2021, the accuracy of OLO was compared with the Sysmex XN-1000 System. Samples – covering a broad clinical range for each tested parameter from 355 males (52%) and 324 females (48%) aged 3 months to 94 years – were analysed. The regression analysis results showed a consonance in correlation coefficient and slope, bias and intercept between OLO and Sysmex XN (Figure 3). Therefore, the study concluded that OLO performs with high accuracy for all CBC parameters and is clinically proven to be substantially equivalent to the gold standard – the Sysmex XN-1000.[2]

FIGURE 3

Meta-analysis plot graphs displaying the results of a method comparison study between the Sight OLO and the Sysmex XN haematology analysers. Graphs indicate Pearson correlation, slope and bias for each parameter. *From AJH 2021;96(10):1269.*



Uncompromising precision at low ranges

In a Sight report summarising the accumulated results from 17 clinical method comparison studies focusing on low counts for clinically significant CBC parameters, OLO also showed an excellent performance in enumerating low ranges (Table 1). The studies compared the performance and accuracy of OLO to comparative haematology analysers (e.g., Sysmex XN and Beckman Coulter DxH models) at various institutes and clinical settings – including oncology departments, an epidemic clinic and central labs of both general and paediatric hospitals – in different countries. Overall, the high agreement between OLO and the comparative analysers and the versatility of technologies, locations, operators, and clinical settings confirmed the robustness and accuracy of OLO across different variables.

TABLE 1

A meta-analysis table from the 17 clinical method comparison studies report showing the correlation, slope, intercept, and bias retrieved between OLO and the comparative analysers for each CBC parameter.

Parameter	N	Range	Correlation	Slope	Slope 95% CI	Intercept	Intercept 95% CI	Relative bias	Relative bias 95% CI
WBC [x10³/µl]	209	0.0 to 4.0	0.989	0.97	(0.95, 0.99)	-0.015	(-0.030, 0.012)	-3.9	(-5.3, -2.0)
HGB [g/l]	344	40.0 to 100.0	0.937	0.96	(0.92, 1.00)	2.57	(-1.00, 6.04)	-1.2	(-2.0, -0.6)
RBC [x10⁶/µl]	499	1.1 to 3.8	0.963	0.96	(0.94, 0.98)	0.117	(0.047, 0.183)	-0.3	(-0.8, 0.0)
PLT [x10³/µl]	135	4.0 to 99.0	0.974	1.01	(0.98, 1.06)	1.7	(0.3, 3.0)	6.5	(4.4, 11.6)
HCT [%]	519	14.0 to 34.9	0.941	0.96	(0.93, 0.99)	0.76	(-0.05, 1.52)	-1.5	(-1.9, -1.2)
NEUT# [x10³/µl]	111	0.0 to 2.0	0.982	0.98	(0.94, 1.02)	-0.006	(-0.052, 0.038)	-2.2	(-4.4, 1.7)
LYMPH# [x10³/µl]	196	0.0 to 1.0	0.931	1.00	(0.96, 1.06)	0.000	(-0.029, 0.023)	0.0	(-2.5, 3.3)

Sight OLO empowers clinicians to provide high-quality patient care

Since OLO leverages AI to produce novel digital pathology, the analyser can produce CBC results within a few minutes at the POC (via a touchscreen interface, printout, email, or LIS/middleware), so there is no need to transport specimens to one central laboratory. By delivering fast yet accurate results – whenever and wherever – OLO allows healthcare providers to efficiently and effectively run their operations without needing to defer to central labs. As a result, this pioneering technology has the potential to speed up diagnosis and ultimately elevate the overall quality of treatment and patient outcomes.

OLO is CE Marked according to the IVD European directive for performing CBC tests in point of care settings. The device is also FDA 510(k) cleared for use in moderately complex settings in the United States. For full indication for use and safety information, please visit the Quality and Compliance page at www.sightdx.com.

Arsenic–ferritin delivery system displays strong anti-leukaemia effect

Using a specifically developed arsenic–ferritin complex, researchers have potentially developed a new targeted delivery system for the treatment of several leukaemias.

With arsenic encapsulated and bound within a ferritin chemical case, researchers have developed a potentially new delivery system for the ion in the treatment of different types of leukaemia.

Leukaemia can be either acute i.e., fast-growing or chronic (slow growing) and there are two main subgroups of acute leukaemia; acute lymphoblastic leukaemia (ALL), frequently diagnosed in children and young adults and acute myeloid leukaemia (AML), which is the most common type in adults.[1]

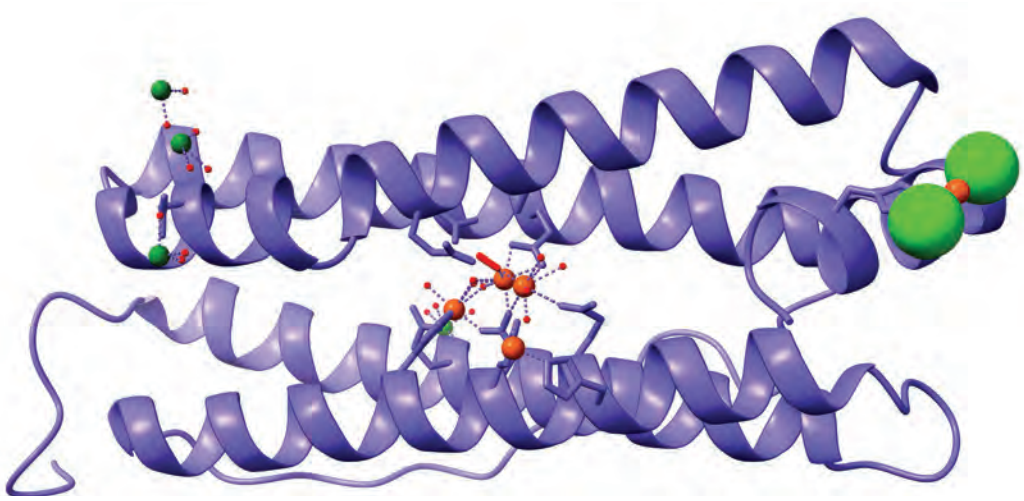
Treatments for AML have increased in recent years, although the cancer has a number of phenotypes and both primary and secondary drug resistance is a problem for many patients.[2] One form of treatment for promyelocytic leukaemia, which is a subtype of AML, is trivalent arsenic (arsenic trioxide, ATO) which is an apoptosis-inducing agent.[3] However, while ATO appears to be effective, a potential difficulty is that the intracellular concentration of the ion within cancerous cells has been found to vary between different form of leukaemia, making it is a less reliable treatment in practice.[4]

In previous work, a team from China had shown that one common feature of different leukaemia cell lines, is over-expression of cell surface receptor termed 'human transferrin receptor 1' (or CD71) and which facilitates the supply of iron into cells upon binding with iron-loaded ferritin. The ferritin molecule itself is a spherical shaped and can serve as a nanocarrier for encapsulated iron oxide particles into peripheral tumours and be used as a treatment for cancer.[5] For the latest study, the Chinese team used the ferritin carrier into which they inserted trivalent arsenic and tested whether this arsenic-ferritin complex, was able to deliver the ion into leukaemia cells.[6]

In their study, the team used animal models to confirm that CD71 was preferentially over expressed on the surface of the cells from different forms of leukaemia, i.e., AML, ALL and chronic myeloid leukaemia in comparison with normal lymphocytes. Secondly, they explored whether the trivalent arsenic could be easily released from the ferritin complex once bound and endocytosed by leukaemia cells. Using HL60 cells, the half-maximum inhibitory concentration value for the arsenic–ferritin complex was 4.9-fold lower than that of conventional arsenic trioxide. Once this had been confirmed, the team measured the concentration of arsenic within cells derived from 167 patients with different leukaemias, it was shown that the arsenic–ferritin complex, released the trivalent ion and led to its accumulation within leukaemia cells.

In their conclusion, the authors noted that the results demonstrated how CD71 was a suitable target because it was preferentially over-expressed in all the forms of leukaemias, even at different stages of the disease.

They suggested that the arsenic–ferritin complex has the potential to become a useful therapy that requires further clinical evaluation in different forms of leukaemia.



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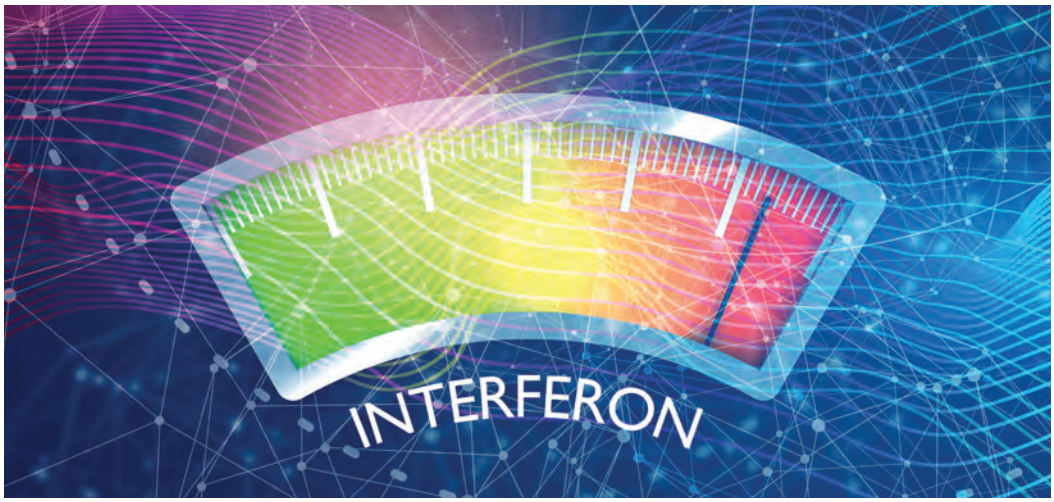
Interferon administration reduces relapse after transplant in leukaemia patients

Interferon given prior to transplantation in high-risk acute myeloid leukaemia appeared to reduce the rate of disease recurrence.



Provision of interferon before transplantation to patients with acute myeloid leukaemia (AML) either not in remission or treatment-resistant, led to reduction in the rate of disease relapse after six months and which was sustained for at least 12 months after the transplant.

This was the finding from a clinical trial conducted by a team from the Division of Haematology-Oncology, University of Michigan, US.[1] Among patients with AML, the most potent therapy is haematopoietic stem cell transplantation (HSCT). Nevertheless, HSCT is deemed to be more toxic than both chemo- and immunotherapy and thus considered as an option for those in whom the estimated survival time and quality of life exceed other treatment.[2] The rationale for HSCT after chemo- or radiotherapy is that the donor T cells, either alone or possibly in combination with other immune cells, help to eliminate any residual leukaemia cells in the recipient; and this response is known as graft-versus-host leukaemia.[3] However, despite the expectation that HSCT is curative, relapse is common with up to 50% of patients experiencing a relapse and 2-year survival rates are below 20%.[4]

For the present study, the US team conducted a Phase I/II trial to evaluate the safety and efficacy of subcutaneous, long-acting formulation of type 1 interferon in reducing relapse among high-risk AML patients, i.e., those not in remission, when they received HSCT. The interferon was administered the day before HSCT followed by three further injections every 14 days. In the first part of the trial, the team determined the maximum tolerated dose of interferon which was 180 micrograms. For the second part of the trial, the primary efficacy endpoint was the cumulative incidence of relapse at six months post-HSCT. The team also considered overall survival (OS) and leukaemia-free survival (LFS) as secondary outcomes.

Findings

A total of 36 patients with a median age of 60 years (39% female) were included in the full study although data for 31 were reported in the Phase II analysis. The cumulative incidence of relapse was 39% (95% CI 24–58%) which was sustained at 1-year. The OS in Phase II was 55% at 6-months and 33% after 2-years. In addition, LFS was 48% at 6-months and 28% after 2-years and there were no differences in either OS or LFS by age or donor type. The authors also reported no apparent safety concerns from using interferon.

Commenting on their findings, the authors noted that with prior studies indicating a relapse incidence of approximately 60%, interferon use appeared to reduce relapse in high-risk patients with AML after HSCT by 20%. Furthermore, OS also appeared to be improved at 33% compared to previously reported figures of between 14 and 26%, although this would require confirmation in further studies. They concluded that their data would require validation in a prospective randomised trial.

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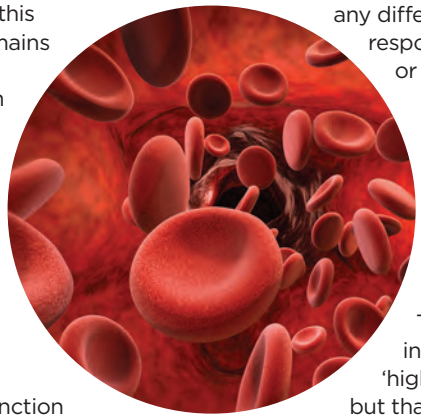
Platelet phenotypes might help personalise treatment and reduce cardiovascular risk

A test that categorises patients into different phenotypes based on the reactivity of their platelets could be used to better understand an individual's response to anti-platelet therapy.

An analysis of patients' platelet function to various agonists important in the clotting process has revealed at least six different phenotypes, potentially leading the way towards more personalised medicine.

This was the finding of a study by a group of researchers from the Institute for Cardiovascular and Metabolic Research, University of Reading, and the Department of Haematology, University of Cambridge.[1] Although platelets have an essential role in haemostasis, these cell fragments are also involved in the clotting process that can lead to a myocardial infarction or stroke. It has been apparent for some time, that an individual's platelet response to clotting agonists can vary,[2] and that these differences might be genetically controlled.[3] Nevertheless, the reasons for this heterogeneity in response remains to be determined and the Reading and Cambridge team wanted to get a better understanding of why an individual might be a hypo-responder to one agonist yet a hyper-responder to another.



In trying to answer this question, the team developed Platelet Phenomic Analysis (PPAnalysis), a platform designed to assess platelet function across a group of individuals.

The PPAnalysis used multiple clotting agonists over a wide range of concentrations to try and fully characterise platelet reactivity. In validating the PPAnalysis system, the researchers recruited a group of healthy, fasted, blood donors and assessed the sensitivity of samples to various agonists as well as the strength (or capacity) of the platelet response. The team used varying concentrations of 6 agonists: collagen-related peptide (CRP), epinephrine, thrombin receptor activator peptide 6 (TRAP-6), U46619 (a thromboxane A2 analogue and adenosine diphosphate (ADP). Together, these agonists allowed the researchers to assess fibrinogen binding and the exposure of P-selectin on the platelet surfaces, which is a marker of alpha-granule secretion, i.e., adhesive proteins that mediate platelet–platelet interactions. In addition, the team recruited a second group of healthy donors, which included non-fasted individuals who were aged between 18 and 75.

Findings

Overall, the study observed that the sensitivity and capacity for fibrinogen binding and the P-selectin exposure did not correlate, in other words, the two measures were independent. In addition, the sensitivity of fibrinogen binding and P-selectin exposure to the individual agonists did correlate ($r > 0.91$, $p < 0.01$) but to a greater degree than the capacity to generate these responses ($r < 0.76$). Nevertheless, the sensitivity to individual agonists did vary, so that one individual could, for example, be highly sensitive to ADP but not be sensitive to CRP. In a separate analysis, the authors did not find any differences between donor responses based on age, gender, or body mass index.

Based on these results, which were replicated in a second, different donor group, the researchers identified at least six different phenotypes with high capacity and low sensitivity and vice versa. These results suggested that individuals were not simply 'high' or 'low' platelet responders but that there was a graded response in between these two extremes. When considering the results from the second group of donors, there was no difference in response.

In discussing their findings, the authors noted that the separation of platelet function into sensitivity and capacity was a novel approach, and which could be of value from a clinical perspective rather than adopting the 'one size fits all' current approach. For example, individuals with a low sensitivity and capacity might be more prone to bleeding when using anti-platelet drugs or in contrast, more treatment resistant when both sensitivity and capacity are high.

While the present study was preliminary, as part of an ongoing programme, the researchers wanted to investigate the association between phenotypic groups using PPAnalysis and the risk of both bleeding and thrombosis in patients.

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Scoring system predicts post-transplant mortality for severe aplastic anaemia patients

A scoring system for post-transplant severe aplastic anaemic patients has shown to be effective in predicting subsequent mortality.

A scoring system that categorises patients with severe aplastic anaemia (SAA) as either low, medium, or high risk of death after haematopoietic stem cell transplant (HSCT) could be of value in clinical practice.

This was the finding of a retrospective analysis by a team from Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Peking, China.

Severe aplastic anaemia represents a rare, life-threatening disease with an estimated prevalence of 1.5–7 cases per million inhabitants per year.[1] Immunosuppressive therapy (IST) would normally be started for patients with SAA, especially in cases where there is no matched sibling donor; however, evidence suggests that up to a third of patients do not respond to IST and also that a third relapse after initial therapy. In contrast, haploidentical donor HSCT is a curative treatment approach for those with SSA especially in the absence of a suitable identical donor and in those who are refractory to IST.[2]

Nevertheless, there are mortality risks associated with HSCT and thus a pre-transplant risk assessment should be undertaken for all patients. Although several risk assessment tools are available, most have been derived from patients with haematological malignancies and none have been validated for patients with SAA. This led the Chinese team to develop a scoring system to enable the prediction of post-transplant mortality incorporating several different factors.[3]

The team turned to data held in a single centre and included all patients who had been diagnosed with SAA and who had subsequently undergone haplo-HSCT. They defined death without disease progression as 'treatment-related mortality' (TRM) and this served as the primary outcome measure. Prior to the transplant, co-morbidities were assessed using the haematopoietic cell transplantation specific co-morbidity index (HCT-CI) and the Eastern Cooperative Oncology group (ECOG) performance status score and for both tools, lower values are associated with a reduced risk. For the purposes of training and validating the predictive model, patients were randomly assigned to either subset, with the training set used to develop the scoring system and the validation cohort to test the model.

Findings

The analysis included 432 patients who were divided into training (288) and validation (144) cohorts. The median age of patients in the training cohort was 16 years (57.6% male) and slightly younger (median age 13 years) and median duration of follow-up was 1131 days. In addition, among those in the training cohort, for 42.7% of patients, the time from SAA diagnosis to HSCT was less than 12 months, with a similar proportion (45.1%) in the validation cohort. The two groups were also matched in terms ECOG and HCT-CI scores prior to their transplant.

In the overall population, the probability of TRM after three years was estimated to be 12% and the 3-year overall survival, was estimated to be 87%. In the predictive model, only three variables were found to be independent predictors of TRM; time for diagnosis to HSCT and both ECOG and HCT-CI scores. Combining these three variables, the authors categorised patients as being at a low, intermediate, and high risk of TRM. Using the model, they calculated the hazard ratio for TRM to be 3.43 for intermediate risk patients and 9.57 for those at high risk when using the low-risk group as the reference point.

The authors concluded that the use of these three parameters would be useful in predicting treatment-related mortality for patients with SAA after HSCT.

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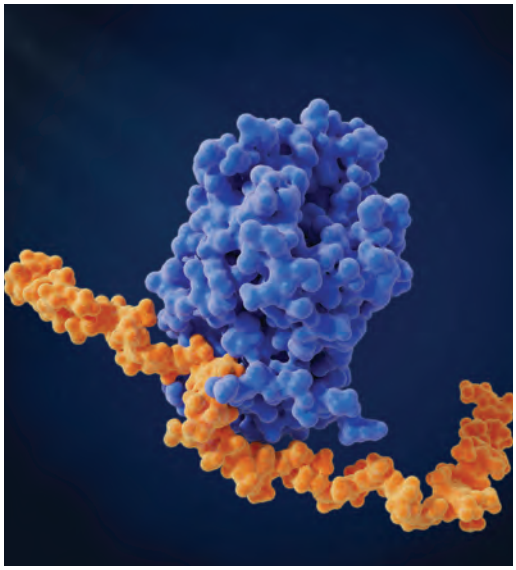
Therapeutic heparin reduces mortality in hospitalised patients with COVID-19

A study among moderately ill patients hospitalised with COVID-19 has revealed how therapeutic as opposed to prophylactic doses of heparin appeared to offer a mortality benefit.

The use of a therapeutic rather than prophylactic dose of heparin provided a mortality benefit to moderately ill, hospitalised patients with COVID-19. This is the key finding of a study by researchers from the Departments of Medicine, and Laboratory Medicine and Pathobiology, University of Toronto, Canada.

The lung changes in patients with COVID-19 has been found to display marked microvascular thrombosis and haemorrhage.[1] In addition, analysis of factors associated with a poor prognosis once infected with the virus include significantly elevated levels of D-dimer and fibrin degradation products.[2] With anticoagulants such as heparin able to reduce D-dimer levels and some evidence of anti-inflammatory activity,[3] these drugs might be of benefit to those hospitalised with COVID-19. However, the currently available evidence is somewhat mixed. For example, in a study of hospitalised, but not critically ill, COVID-19 patients, therapeutic doses of heparin increased the probability of survival,[4] whereas in contrast, among hospitalised but critically ill patients, heparin was not beneficial.[5]

With some uncertainty over the possible advantages of heparin among those hospitalised with COVID-19, the Canadian team established the Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 pandemic (RAPID) trial.[6] The overarching aim of the trial was to determine whether therapeutic rather than prophylactic doses of heparin were superior in reducing the composite of admission to an intensive care unit (ICU), mechanical ventilation or death, in moderately ill hospitalised COVID-19 patients with elevated D-dimer levels. The RAPID trial enrolled patients who were admitted to a hospital ward (but not ICU) and not mechanically ventilated, with elevated D-dimer levels (above the upper limit of the normal range) within the first five days of admission. Patients were randomised 1:1 to therapeutic or prophylactic heparin with the former representing a higher dosage. For example, using enoxaparin, a therapeutic dose for a patient with a body mass index less than 40 would be 1mg/kg every 12 hours. In contrast, the prophylactic dose for a patient of the same weight would be 40mg every 24 hours. The primary outcome of the study was a composite of ICU admission, non-invasive or invasive mechanical ventilation or death up to 28 days. There were several secondary outcomes including all-cause mortality, ICU admission, ventilation-free days alive, need for renal replacement therapy etc.



Findings

A total of 465 patients with a mean age of 60 years (56.7% male) and with 42.3% of White ethnicity were randomised to either dose of heparin. The main co-morbidities included hypertension and diabetes and baseline D-dimer levels were 2.3-fold above the upper limit for normal.

The primary outcome occurred in 16.2% of those assigned to therapeutic heparin and 21.9% given a prophylactic dose and this difference was not statistically significant (odds ratio, OR = 0.69, 95% CI 0.43–1.10, p = 0.12). In contrast, all-cause mortality occurred in 1.8% of the therapeutic and 7.6% of the prophylactic groups (OR = 0.22, 95% CI 0.07–0.65, p = 0.006). There were no differences in secondary outcomes apart from the mean number of ventilation-free days although this was borderline (p = 0.042).

Commenting on their findings, the authors noted that while there was no difference in the primary outcome, the 78% lower mortality among those given therapeutic heparin was significant. Based on these findings, they concluded that therapeutic heparin is beneficial in moderately ill patients with COVID-19.

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Using precision medicine improves PFS in haematological cancers

Using a single-cell functional precision medicine approach for those with advanced, aggressive haematological cancers has been found to be feasible and effective approach to patient management.

A personalised approach to therapy improves progression-free survival (PFS) in patients with advanced and aggressive haematological cancers. This was the conclusion of a small study by researchers from Department of Medicine, Division of Haematology University of Vienna, Austria.

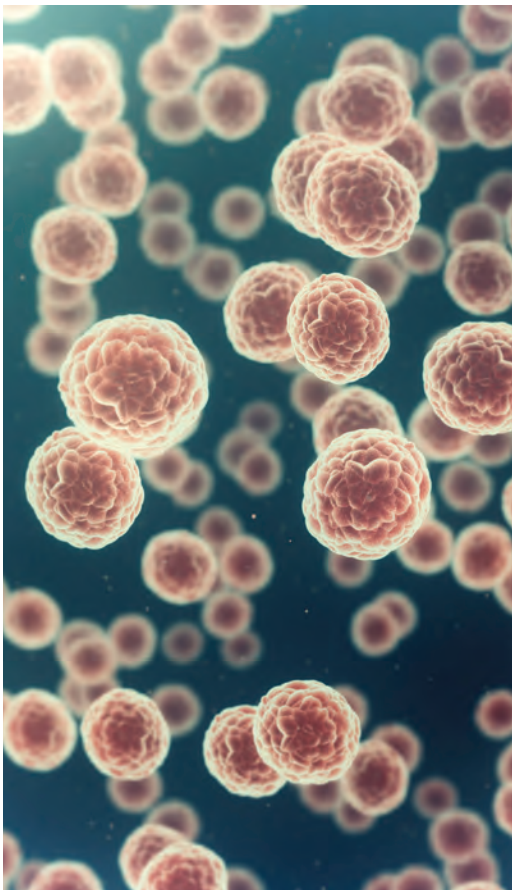
The purpose of precision medicine is to ensure that treatment is individualised and, in recent years, molecular profiling has enabled the gathering of treatment-related information to guide patient management. In the cancerous process, a normal cell undergoes a series of genomic changes leading to the production of aberrant proteins which serve as a target for molecular agents. In fact, evidence suggests that matching therapy to a genetic aberration is associated with a higher overall response rate[1] and this treatment matching has already been successfully employed in some haematological cancers such as the BRAF inhibitor, vemurafenib, in hairy cell leukaemia.[2]

For the present study,[3] the Austrian researchers took a slightly different approach and used a technique termed 'imaged-based single cell functional precision medicine' (scFPM). This involves removal of cells from a biopsy sample and then analysing the response of target proteins produced by these cells to a range of different anti-cancer drugs, thus helping to guide treatment-related decisions.

Patients included had aggressive haematological cancers and had received at least two standard courses of treatment prior to entry or no standard therapy options. The primary outcome of interest was the PFS ratio, defined as scFPM/PFS on previous treatment, with the outcome set as a ratio value greater than 1.3 which was considered beneficial.

Findings

A total of 143 patients were enrolled, of whom 56 received treatment based on the results of scFPM and 20 received physician-directed treatment and hence served as a control. In the cohort of 56 patients, the median age was 64 years (63% male) and the median follow-up time for all patients was 718 days. Haematological cancers included acute myeloid leukaemia (25%), aggressive B-cell non-Hodgkin lymphoma (46%) and T-cell non-Hodgkin lymphoma (28%) all of which were aggressive and without a standard treatment option.



There were 30 (54%) of the 56 patients who met the primary endpoint of a PFS ratio > 1.3 with a median PFS ratio of 3.4. In other words, patients treated via scFPM guided therapy experienced a three-fold greater PFS response compared to their previous treatment. In addition, 13 (23%) of patients were progression free after 12 months on scFPM-guided therapy, compared with only three on previous treatment and the objective response rate was 55% of those on scFPM guided therapy.

In discussing their findings, the authors noted that scFPM guided therapy can be easily incorporated to the clinical workflow and was of benefit to patients with late-stage blood cancer.

They concluded that this initial study has paved the way for prospective randomised trials comparing scFPM-guided therapy with comprehensive genomic profiling as a physician's choice.

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Crizanlizumab approved by NICE for managing sickle cell crises

NICE has approved crizanlizumab for sickle cell crises in patients with sickle cell disease but only as part of a managed access agreement.

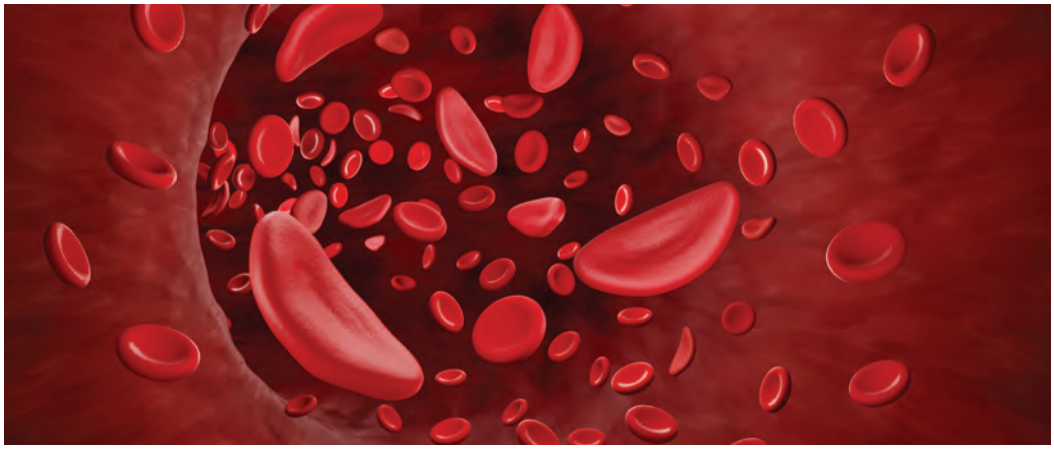
The National Institute for Health and Care Excellence (NICE) has given the green light to crizanlizumab for the management of sickle cell crises in people with sickle cell disease. The term sickle cell disease[1] describes a group of inherited red blood cell disorders that affect haemoglobin and for which, according to the World Health Organization, approximately 5% of the world's population carries trait genes.[2] Sickle cell disease affects around 1 in 500 African American children and 1 in 36,000 Hispanic American children and is characterised by a change in the shape of red blood cells which become more 'sickle-like", reducing their flexibility of the cells.[3] These sickle-like red blood cells can lead to recurrent and unpredictable blockage of small blood vessels[4] producing ischaemic pain, referred to as vaso-occlusion (VOC) or sickle cell crises. In addition, activated and adherent leukocytes are the likely drivers of VOC in collecting venules and this process appears to be initiated by a transmembrane protein, P-selectin.[5] Studies have shown that blockage of P-selectin appears to improve blood flow,[6] and thus reduce the risk of VOC and sickle cell-related pain crises.

Clinical efficacy

The monoclonal antibody crizanlizumab binds to P-selectin, thereby blocking its action. The approval by NICE was based on data from the SUSTAIN trial.[7] This double-blind, randomised, placebo-controlled, Phase II trial, assigned 198 patients to either a low-dose crizanlizumab (2.5mg/kg body weight), a high-dose crizanlizumab (5.0mg/kg), or placebo and which were administered intravenously 14 times over a period of 52 weeks. The primary outcome was the annual rate of sickle cell–related pain crises with high-dose crizanlizumab versus placebo. For the study, this was defined as acute episodes of pain caused by a VOC that resulted in a visit to a medical facility and treatment with pain relief medication. The results showed that the median rate of crises per year was 1.63 with high-dose crizanlizumab versus 2.98 with placebo (p = 0.01). In addition, the median time to the first crisis was significantly longer with high-dose crizanlizumab than with placebo (4.07 vs. 1.38 months, p = 0.001), as was the median time to the second crisis (10.32 vs. 5.09 months, p=0.02). In addition, the overall incidence of serious adverse event was comparable across the three arms.

NICE recognised that a limitation of the trial was the absence of longer-term data on crizanlizumab, such as mortality or among those who did not seek medical advice on VOCs. There was also no data on the prolonged treatment benefit and what happens when patients stop taking crizanlizumab.

While the appraisal document[8] concluded that "crizanlizumab is not recommended for routine use in the NHS", the drug could be used where specific criteria are met. Thus, guidance notes that "crizanlizumab is recommended as an option for preventing recurrent sickle cell crises (vaso-occlusive crises) in people aged 16 or over with sickle cell disease only if the conditions in the managed access agreement are followed."



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