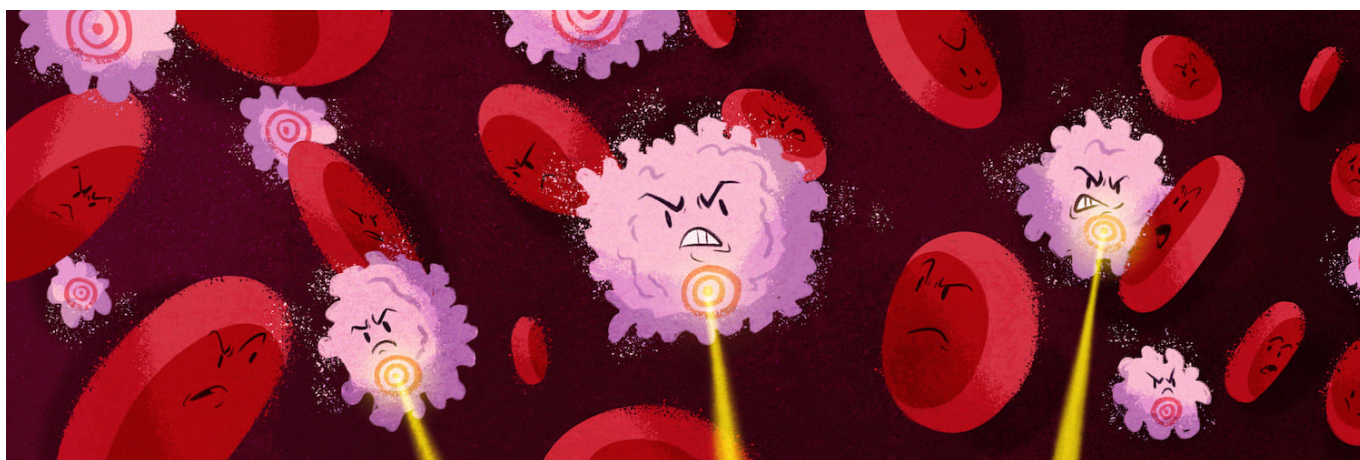


Cancerworld

Highlights of 2020 American Society of Hematology (ASH) meeting

Janet Fricker / 14 January 2021



Like most 2020 meetings the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition, held 5-8 December, was hosted virtually. Due to meticulous planning, the format did not prevent delegates attending the largest gathering of the professional haematology community from undergoing the full conference experience. There was a wide ranging and innovative scientific programme, a virtual exhibit hall, satellite symposiums and even a central hub allowing networking. Here, *Cancer World* highlights the haematological cancer presentations that we believe will have the greatest impact on patient care.

Age no barrier for stem cell transplant in myelodysplastic syndrome

Older patients with high-risk myelodysplastic syndromes (MDS) achieve a survival benefit from stem cell transplant. [The study](#), conducted by the US Blood and Marrow Transplant Clinical Trials Network, concluded allogeneic haematopoietic cell transplantation (HCT) should be offered to all individuals aged between 50 and 75 years for whom suitable donors can be identified.

“It is important to refer these patients early so the transplant centre can work on finding an optimal donor right from the get-go,” said senior author Corey Cutler (Dana-Farber Cancer Institute, Boston, US).

Despite HCT being the only curative therapy for MDS, the procedure is not generally offered to older patients due to the lack of evidence from clinical trials.

For the study, 384 patients with intermediate or high risk MDS seen at 34 medical centres, and aged between 50 and 75 years, were enrolled prior to searches for a donor. Altogether, 260 subjects were

matched to donors and received transplantation, while 124 failed to achieve a match, and received standard supportive care (mainly treatment with hypomethylating agents).

Results showed adjusted overall survival (OS) at three years was 47.9% for those in the donor arm versus 26.6% for those without a donor ($P=0.0001$, absolute difference 21.3%, 95%CI 10.2%–31.8%). Additionally, leukaemia-free survival (LFS) was 35.8% in the donor arm versus 20.6% in the no donor arm ($P<0.0001$). Both OS and LFS benefits were observed across all sub-groups tested for those receiving transplants, and both groups reported similar quality of life (assessed by a range of scales including the Functional Assessment of Cancer Therapy: General total score, SF-36 Physical and Mental Components, and EQ-5D).

“Bone marrow transplant will be the standard of care, rather than drug therapy, for those high-risk patients with MDS who can receive a transplant,” commented ASH spokesperson Robert Brodsky (John Hopkins School of Medicine, Baltimore, US).

Discovery of childhood origins of myeloproliferative neoplasms provides opportunities for prevention.

Genetic mutations linked to myeloproliferative neoplasms (MPS) may occur during childhood or before birth and proliferate for years prior to onset of cancer. [The late-breaking study](#), establishes a new paradigm for development of blood cancers, refuting the common assumption that cancers are diagnosed within a few years of emergence, and suggests genetic tests could be used much earlier, providing opportunities to prevent cancer development.

“We were not expecting this. In fact, in one patient the *JAK2* mutation was acquired more than 50 years before their diagnosis,” said lead author Jyoti Nangalia (Wellcome Sanger Institute, Cambridge, UK).

Mutations in cancer-associated genes drive tumour outgrowth, yet little is known about the chronology of driver mutations and dynamics of clonal expansion that lead to human cancers.

For the study, Nangalia and colleagues focused on a cohort of 10 patients with essential thrombocythaemia (ET), polycythaemia vera (PV), and myelofibrosis (MF), who had been diagnosed at between 20 and 75 years of age. For each patient, peripheral blood and bone marrow samples were grown into single cell-derived haematopoietic colonies, with each colony undergoing whole-genome sequencing. Altogether, 952 whole-genome sequences were produced, each reflecting the single cell from which the colony was derived. By assessing the hundreds of thousands of mutations patients naturally acquired, the team were able to trace the ancestry of different blood cells and estimate the time when they acquired mutations. Results showed:

- The mean latency between *JAK2* acquisition and clinical presentation was 34 years (range 20–54 years).
- In a patient diagnosed with ET aged 21 years, the *JAK2* mutation was acquired between 6.2 weeks post-conception and 1.3 years of age.
- In a patient diagnosed with PV aged 31 years, the *JAK2* mutation was acquired between 4.2 weeks post-conception and 8.6 years of age.
- In a patient diagnosed with PV aged 33, the *JAK2* mutation was acquired between 9.1 weeks post-conception and 4.1 months after birth, and the *DNMT3A* mutation between 19 weeks and 22.2 weeks post conception.

The next step, explained Nangalia, will be to explore factors influencing different rates of cancer growth, and determine whether there might be ways to intervene and slow the growth of cells with

cancer-linked mutations.

Commenting on the study in a press briefing, ASH spokesperson Robert Brodsky said, “These results suggest that there may be untapped opportunities to detect these conditions much earlier and potentially intervene and prevent disease development.”

Registry provides information on Covid-19 and blood cancers

Patients with haematologic malignancies represent a ‘medically vulnerable’ population at increased risk for significant Covid-19 morbidity and mortality. [The registry study](#) found risk of death was greatest among those who were older, had more severe infections, poorer prognosis, or who decided to forego intensive treatment.

The American Society of Hematology Research Collaborative (ASH RC) launched the ASH RC COVID-19 Registry on April 1 2020 to collect data from patients of all ages with a Covid-19 diagnosis and underlying haematological disorders. “The idea basically was to try to get information to providers as quickly as possible about patients who have Covid-19 and blood cancers,” said William Wood (University of North Carolina, Chapel Hill, North Carolina), the study presenter. The establishment of a registry was all-important for blood cancers, since many patients have underlying immune dysfunction, and furthermore are treated with chemotherapies and immunotherapies that are immunosuppressive. The registry information will be used for risk stratifying patients, planning resource allocation and designing future clinical trials.

In the session, Wood updated the published abstract, reporting on 656 patients from more than 100 centres worldwide (including 396 patients from North America). Regarding cancer types, 57% had leukaemia, 25% had lymphoma, and 18% had plasma cell neoplasms. For the registry, patients were categorised into three groups according to Covid-19 severity - mild requiring outpatient care ($n=227$); moderate, requiring hospitalisation ($n=228$); and severe, requiring intensive care admission ($n=136$).

Results showed:

- The overall death rate for all patients with haematologic malignancies was 20%, a figure considerably higher than the 2% case-rate found in the general US population.
- The effect of age. Prevalence of moderate or severe illness increased according to age, affecting 47% for those aged 19–39 years; 62% for those aged 40–69 years; and 70% for those older than 70 years. Additionally, mortality rates for patients with moderate to severe illness also increased with age: 6% for those aged 19–39 years; 18% for those aged 40–69 years; and 33% for those older than 70 years.
- Pre-Covid-19 prognosis related to severity of infection. Among patients expected to live >12 months, 58% developed moderate or severe illness and 13% died; whereas for those expected to live <12 months, 79% developed moderate or severe illness and 51% died.
- Mortality rates differed according to malignancy status: 13% of those in remission died compared to 21% for those undergoing initial cancer treatment and 36% for those with relapsed or refractory haematologic cancers.
- A link between COVID-19 mortality and lack of intensive care unit (ICU) care. Patients who declined ICU had a mortality rate of 73% versus 13% for patients who experienced ICU care.

Data collection for the ASH registry is ongoing. “We encourage data submission and welcome participation from you all,” said Wood. Information about contributing to the ASH registry can be accessed [here](#).

Studies point to future of CAR T cell therapy

The next chapter in the CAR T story was outlined in a number of presentations at ASH. The wide ranging studies included new indications for CAR T cell treatment, ways to enhance response and future technological innovations in the construction of CAR T cells.

Chimeric antigen receptor T-cell (CAR T) therapy has emerged as a therapeutic T cell engineering practice, where T cells derived from patient blood are genetically engineered to express artificial receptors targeted to specific tumour antigens. To date, three CAR T-cell therapies have been approved – axicabtagene ciloleucel for adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy; brexucabtagene autoleucel for adults with relapsed or refractory mantle cell lymphoma; and tisagenlecleucel for adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy and for people up to 25 years with B-cell precursor acute lymphoblastic leukaemia. All therapies target the CD19 antigen expressed by most B-cell cancers. At ASH 2020 a range of noteworthy CAR T-cell studies were presented including:

- The ZUMA-12 study, which assessed axicabtagene ciloleucel as part of front line therapy for high risk patients with large B-cell lymphoma (LBCL). The interim analysis [of the phase II open label study](#) ($n=15$ patients), showed 85% of patients experienced overall response, and 74% experienced complete response. Additionally, 70% of patients enrolled had an ongoing response at the data cut-off after median follow-up of 9.3 months. Researchers found blood peak levels of CAR T cells and median CAR T cell expansion were higher in the ZUMA-12 study than the ZUMA-1 study, where immunotherapy products were generated from patients who had received several lines of chemotherapy. “This trial is a step toward moving CAR T cell therapy to first-line therapy for patients with aggressive B-cell lymphoma,” said principal investigator Sattva Neelapu (University of Texas MD Anderson Cancer Center, Houston).
- The ZUMA-5 trial reporting the first data for CAR T therapy in relapsed/refractory indolent non-Hodgkin lymphoma (iNHL). In [the phase II study](#), investigators administered axicabtagene ciloleucel to 146 patients, including 124 with follicular lymphoma (FL) and 22 with marginal zone lymphoma (MZL). Overall, 92% achieved an objective response (94% with FL; 85% with MZL) and 76% achieved a complete response (80% with FL and 60% with MZL). “Based on the safety profile we observed, we plan to evaluate the potential for outpatient treatment with axicabtagene ciloleucel in indolent lymphoma,” said presenter Caron Jacobson (Dana Faber Cancer Institute, Boston, Massachusetts).
- The first in human study for CAR T therapy targeting both CD19 and CD20 antigens. The [phase I study](#) represents a bid to overcome the possibility of antigen-escape and subsequent relapse, and involved 12 elderly patients with relapsed or refractory B-cell non-Hodgkin lymphoma. Peter Borchmann (University Hospital of Cologne) reported that five patients achieved complete response and had an ongoing response up to 14 months at data cut-off. There were no dose-limiting toxicities, severe (grade three or worse) cytokine release syndrome (CRS) or neurotoxicity, although CRS of any grade occurred in 58% of patients.
- The first study combining CAR T-cell therapy with CRISPR-Cas9 gene editing technology to improve response. In [abstract 554](#), Marco Ruella (University of Pennsylvania, Philadelphia) reported on a mouse model of T-cell leukaemia using CRISPR-Cas9 technology to knock out the CD5 gene found on the surface of CAR T cells to create the new therapy MB-CART2019.1. It has been suggested that the presence of CD5 may inhibit activation of T cells and explain why CAR T therapy has not proven effective in haematological malignancies expressing high CD5 levels (e.g. T cell lymphoma and leukaemia). Results demonstrated mice infused with MB-CART2019.1 showed higher levels of T cell proliferation in peripheral blood, as well as a significant reduction in tumour size and better survival outcomes compared to mice infused with non-edited CAR T cells. “We’ve shown, for the first time, that we can successfully use

CRISPR-Cas9 to knockout CD5 on CAR T cells and enhance their ability to attack cancer,” said Ruella.

Illustration by: Maddalena Carrai