Improved Outcomes in Leukemia, Trauma Settings with Personalized Medicine Approaches: Program

This session features studies showing new means of treating hematologic illnesses by tailoring medicines to patients' specific disease characteristics. Two abstracts show that patients with chronic myeloid leukemia may be able to safely reduce their use of tyrosine kinase inhibitors, a treatment mainstay for years, potentially reducing the side effects and costs associated with these diseases. Another shows that a prototype medical device could, with less than a drop of blood, quickly provide a complete report on a patient's blood clotting status and transform care in the trauma setting.

Julie Jaffray, et al.

419 Easy-to-Place Intravenous Lines May Come at a Cost: Study Finds PICCs Associated with a Greater Risk of Blood Clots in Kids

Conclusion:[nbsp]

This is the first prospective pediatric study comparing VTE incidence in PICCs versus TLs. This interim analysis of nearly 800 subjects revealed a significantly higher risk of VTE in subjects who have had a PICC placed versus a TL. Due to their ease of insertion, PICCs are being placed at increasing rates in some pediatric centers, thus this finding may be the leading factor for the increasing pediatric VTE incidence. Other significant risk factors for VTE were patients with multiple lumen CVCs and a history of VTE. For children who require a new CVC, practitioners should consider avoiding PICCs and multiple lumen CVCs if possible. Consideration should also be made to give prophylactic anticoagulation for children with a CVC and a history of VTE. Further analysis will be performed concerning the decreased VTE rate in male patients.

The identification of these risk factors is the first step to creating CVC selection and insertion guidelines for all children to prevent VTE. Continued subject recruitment, with the recent addition of Nationwide Children's Hospital, is occurring to complete this evaluation.

ASH Press Release: When treating kids with cancer, congenital heart disease, infections, or other serious health problems, care teams often need to insert a thin, flexible tube (called a catheter) into a large central

vein to allow them to easily administer medications and quickly draw blood, while also avoiding multiple needle sticks. New data suggest that the type of central line used — whether it is inserted in the arm or closer to the heart — may make a difference when it comes to a child's risk of developing blood clots.

In the first prospective, multicenter pediatric study to compare the occurrence of blood clots in children receiving peripherally inserted central catheters (PICCs) or centrally inserted tunneled lines (TLs), 85 percent of blood clots observed were in children who had a PICC placed.

"An overwhelming number of blood clots happen in patients with PICCs placed when compared to tunneled lines," said senior study author Julie Jaffray, MD, of Children's Hospital Los Angeles. "We know children with cancer or who are in the pediatric intensive care unit will need a central line placed. But these lines aren't perfect. The important question is: are we choosing the right line for them or are we just putting in the line that's easier to place?"

Part of the draw to using PICC lines is that they are much easier to put in; they can be inserted at the bedside with a touch of sedation if needed. For tunnel lines, patients are booked for anesthesia and a surgeon or interventional radiologist is needed to place the tube.

This interim analysis was based on 1,096 children, who had a total of 1,233 central venous catheters placed (67% PICCs and 33% TLs) at Children's Hospital Los Angeles, Children's Hospital of Philadelphia, Texas Children's Hospital, and Nationwide Children's Hospital between September 2013 and April 2016. Patients ranged in age from 6 months to just under 18 years old. A total of 65 blood clots were identified during follow up, 55 of which were in children with PICCs. The median time to developing a blood clot after a PICC was placed was 15 days; the median time to develop a blood clot after a TL was placed was 40 days. Forty-nine percent of the central venous catheters were removed before six months. The average time a central venous catheter was in place, which includes both PICCs and TLs, was 56 days.

The data also show that children with congenital heart disease, who already have abnormal blood circulation, and those with cancer, especially with leukemia, have a greater risk. The use of multiple lumen venous lines (those with two or more "branches" of tubes) was also associated with a higher risk of clots. Similarly, blood clots were four times more likely to occur if the patient was diagnosed with a central line infection; infections were significantly more likely with tunnel lines.

PICCs are increasingly being used in many pediatric centers — a trend Dr. Jaffray said has paralleled a noticeable rise in the number of blood clots seen in children and was the main impetus for this research. The study will continue to accrue patients and additional analyses will show whether the main reason for inserting the line (e.g., chemotherapy, prolonged courses of antibiotics, or feeding) plays a role. Researchers said the findings will help inform the first guidelines on how to use and select central venous lines in children and when anticoagulants might be advised to prevent blood clots.

Julie Jaffray, MD, Children's Hospital Los Angeles and University of Southern California, Los Angeles, will present this study during an oral presentation on Sunday, December 4 at 5:30 p.m. in Ballroom 20BC of the

San Diego Convention Center.

Webcast:

Harry P. Erba, et al.

211 A Phase 1b Study of Vadastuximab Talirine in Combination with 7+3 Induction Therapy for Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

Conclusions: 33A can be safely combined with 7+3 with acceptable count recovery and the recommended phase 2 dose is 20+10 mcg/kg on Days 1 and 4. An alternate schedule of single-day dosing on Day 1 is under investigation and enrollment continues. Extramedullary AEs, including hepatic toxicity, and induction mortality rates were similar to reported rates for 7+3 alone in this AML population. A high remission rate within the 1st induction cycle was observed, the majority of which were MRD negative.

ASH Press Release: In a clinical trial, vadastuximab talirine (33A) was found to be safe when used in combination with standard chemotherapy treatment for patients with acute myeloid leukemia (AML). The trial results raise researchers' hopes that this investigational, targeted therapy can help patients achieve more complete cancer remission and reduce the likelihood of relapse.

33A is being developed as a complement to standard chemotherapy in an effort to reduce the need for multiple rounds of chemotherapy to induce initial remission and to improve long-term outcomes. The standard treatment for AML, which consists of a continuous infusion of cytarabine for seven days plus infusion of an anthracycline for three days (often called 7+3), has been in use for decades but achieves an overall cure rate of just 40–50 percent in patients younger than 60 years. 33A is designed to seek out CD33, a protein found on leukemic blasts in roughly 90 percent of AML patients, and kill these targeted cells.

This Phase 1b study included 42 patients who were administered 33A along with standard chemotherapy. Patients showed no evidence of increased toxicity or mortality, and the rates of adverse effects were similar to what would be expected with standard chemotherapy alone, according to the researchers. No patients experienced infusionrelated reactions, venoocclusive disease, or significant liver damage. The most commonly reported side effects were nausea (reported by 55% of patients), diarrhea (33%), and constipation (31%).

Researchers said the outcomes were also encouraging from an efficacy standpoint because a higher-than-expected portion of patients achieved remission after a single round of treatment. A total of 78 percent of

patients achieved remission, with 60 percent achieving complete remission (CR) and 18 percent achieving remission with incomplete blood count recovery (CRi). In addition, highly sensitive tests showed many patients had no evidence of the disease 28 days after starting treatment, suggesting the drug may lead to a more complete remission than standard chemotherapy alone.

“I think we can safely give vadastuximab talirine in combination with chemotherapy,” said lead study author Harry Erba, MD, PhD, of the University of Alabama at Birmingham. “The next question to study is whether it improves long-term disease-free survival. There’s much reason to be hopeful that such an investigation will have positive results.”

Funding for this study was provided by Seattle Genetics.

Harry Erba, MD, PhD, University of Alabama at Birmingham, will present this study during an oral presentation on Saturday, December 3 at 4:00 p.m. in San Diego Ballroom AB of the Marriott Marquis San Diego Marina.

Webcast:

Richard E. Clark, et al.(Mhairi Copland, Presenting)

938 Chronic Myeloid Leukemia Patients with Stable Molecular Responses (at least MR3) May Safely Decrease the Dose of Their Tyrosine Kinase Inhibitor: Data from the British Destiny Study

Conclusion: In CML patients with stable MR3 or better, decreasing TKI treatment to half the standard dose appears safe, and is associated with improvement in TKI related side effects, implying that many patients with stable responses are being overtreated. Studies of more ambitious de-escalation are warranted.

ASH Press Release: A study led by researchers at the University of Liverpool, United Kingdom, suggests many CML patients may be able to safely reduce TKI side effects by cutting their dose in half. In contrast to other trials, which focus on patients who are nearly free of leukemia as measured by very sensitive tests, the new study included some patients with a stable molecular remission level demarcated according to international standards as MR3 — a level the researchers describe as “good, but not perfect.” The results suggest that a wider range of patients may be able to safely reduce TKI therapy than was previously thought feasible.

Of 174 study participants, the vast majority (93%) showed no evidence of leukemia rebound one year after cutting their TKI dose, and many reported a significant decrease in TKI-associated side effects within the first three months. Just 12 participants showed signs of leukemia recurrence, all of whom regained a remission level of MR3 or better within four months of resuming a full TKI dose.

“Taken together, these findings might indicate that some patients are being unnecessarily over-treated,” said study author Mhairi Copland, MD, PhD of the Institute of Cancer Sciences, University of Glasgow, United Kingdom. “The other important implication is that patients do not have to have extremely low levels of leukemia on very sensitive tests in order to safely try reducing their TKI dose.”

Participants who started with extremely low levels of leukemia (MR4) were significantly less likely to experience a leukemia rebound (seen in 2.4% of these patients) compared with those classified as MR3 (18.4%), but Copland said the low rates of rebound overall suggest it is safe for MR3 patients to attempt to reduce their TKI dose if desired. Any benefits in terms of reducing side effects should become apparent within the first three months.

The study received funding from the University of Newcastle, United Kingdom, and from the U.K.-based blood cancer charity Bloodwise.

Mhairi Copland, MD, PhD, University of Glasgow, United Kingdom, will present this study during an oral presentation on Monday, December 5 at 3:00 p.m. in Pacific Ballroom 18–19 of the Marriott Marquis San Diego Marina.

Webcast:

Francois-Xavier Mahon, et al.

787 Cessation of Tyrosine Kinase Inhibitors Treatment in Chronic Myeloid Leukemia Patients with Deep Molecular Response: Results of the Euro-Ski Trial

Conclusions: Using standardized molecular monitoring, stopping TKI therapy in a very large cohort of CML-patients appears feasible and safe and high MRFS rates are achievable. Longer duration of imatinib-therapy (optimal ≥ 5.8 years) prior to TKI-stop is associated with a higher probability of MRFS. Taking into account the long follow-up without molecular relapse in the historical studies such as STIM1 (Etienne et al; JCO 2016) the “operational” cure of CML with oral TKI is an up-to-date issue.

ASH Press Release: Drugs known as tyrosine kinase inhibitors (TKI), including imatinib, nilotinib, and

dasatinib, are so effective at controlling chronic myeloid leukemia (CML) that some patients seek to avoid the drugs' side effects and save costs by reducing the TKI dose or discontinuing TKI treatment altogether once they have achieved a stable level of leukemia remission. Thanks to these drugs, the life expectancy of patients with CML now approaches the life expectancy of the general population.

Although the drugs are highly effective at keeping leukemia in check, their side effects and cost have led some patients and their doctors to question whether it would be feasible to discontinue their use after a patient achieves consistently negative leukemia test results.

Under current guidelines, most patients who achieve remission with TKI therapy are advised to continue taking the drugs indefinitely, yet it is unclear whether continued therapy is necessary for all patients. Common side effects include cramps, fluid retention, excess fluid around the lungs, skin rashes, nausea, vomiting, diarrhea, damage to the heart, and fatigue, and women are typically advised not to conceive children while taking the drugs due to the high risk of birth defects.

Cessation of Tyrosine Kinase Inhibitors Treatment in Chronic Myeloid Leukemia Patients with Deep Molecular Response: Results of the Euro-Ski Trial [787]

In one of the largest ever trials to assess the safety of stopping TKI therapy, about half of 821 CML patients showed no evidence of relapse two years after treatment cessation, suggesting that some patients can safely discontinue TKI use.

Study participants who had taken a TKI for more than 5.8 years before stopping were significantly less likely to experience relapse within the first six months (relapse occurred in 34.5% of these patients) compared to those who had been on the therapy for a shorter duration (57.4%), according to the research team. Each additional year of TKI therapy increased a patient's chances of successful TKI discontinuation by about 16 percent.

The study focused on CML patients whose leukemia was in deep remission. All participants had a stable, extremely low level of detectable leukemia markers for at least one year before TKI cessation. After stopping TKI therapy, 62 percent showed no evidence of leukemia recurrence at 6 months, and half (52%) showed no recurrence at 24 months.

Of the patients who experienced leukemia recurrence, most regained their previous remission level after resuming TKI therapy and no study participants, within the study follow-up period, progressed to a dangerous state of advanced disease.

"Many patients struggle between the decision to stop TKI use because of its side effects and the fear of remission. Because of the high number of patients included in this study, we think the results could help to inform future guideline recommendations for TKI use," said lead study author Francois-Xavier Mahon, MD, PhD of the Bergonie Cancer Center of the University of Bordeaux, France.

This study was supported by European Leukemia Net (ELN) and was partially funded by the French National Institute of Cancer (INCA).

Francois-Xavier Mahon, MD, PhD, Bergonie Cancer Center, University of Bordeaux, France, will present this study during an oral presentation on Monday, December 5 at 10:30 a.m. PST in Pacific Ballroom 18–19 of the Marriott Marquis San Diego Marina.

Webcast:

Evi X. Stavrou, et al.

3754 A Miniaturized Microfluidic Dielectric Sensor for Point-of-Care Assessment of Blood Coagulation

Conclusion: We have developed a novel dielectric microfluidic sensor (ClotChip) that is sensitive to multiple coagulation factors and platelet activity, thereby allowing whole blood assessment of hemostasis in a single disposable sensor. The ClotChip will bring blood coagulation testing closer to the patient for time-sensitive applications such as diagnosis of the bleeding patient and in trauma-induced coagulopathy.

ASH Press Release: With less than a drop of blood, a prototype for a portable, disposable sensor provides a complete report on a patient's ability to clot blood in less than 15 minutes. The unique device, called ClotChip, provides a rapid, point-of-care assessment of the integrity of clotting factors and platelet activity. Currently, such results are obtainable only with specialized laboratory testing.

The device could be game-changing in acute emergencies when doctors need to know if a bleeding patient has taken anticoagulant or antiplatelet medications to assess whether an antidote is needed to reverse the drug's effects. Accurate information about blood clotting activity is associated with better survival. ClotChip could also be used to assess a patient's response to anticoagulant or antiplatelet therapy at the point of care in order to assist physicians in determining if a medication requires dose adjustment.

The device has the potential for use in health-care settings that lack easy access to specialized laboratory testing. Unlike standard blood coagulation and platelet testing procedures that use specially trained personnel, large machines, and blood samples collected in a special way, ClotChip uses a fully electrical technique called dielectric spectroscopy to detect markers of coagulation activity in real time.

The investigators compared ClotChip to conventional tests using blood samples from 11 healthy individuals and 12 people with blood clotting disorders such as hemophilia. ClotChip showed a higher

degree of sensitivity than conventional screening tests for coagulation defect diagnosis. When compared to conventional tests, ClotChip showed a reduced rate of false negative results.

“Our device gives you different information—and more information—than other devices out there,” said lead study author Evi X. Stavrou, MD, of Case Western Reserve School of Medicine, Cleveland, Ohio. “The sensitivity and discriminatory ability of the device, when compared to standard coagulation tests, is what excites me very much.”

The researchers are currently recruiting volunteers to participate in an expanded round of testing for the device. The team is also working to optimize the device’s construction in order to enhance its sensitivity.

Partial support for this project has come from the Case-Coulter Translational Research Partnership and the Advanced Platform Technology Center, a Veterans Affairs Research Center of Excellence at Case Western Reserve University.

Evi X. Stavrou, MD, Case Western Reserve School of Medicine, Cleveland, Ohio, will present this study during a poster presentation on Monday, December 5 at 6:00 p.m. in Hall GH of the San Diego Convention Center.

Webcast: