October 24, 2014 - Friday

Turkish Society of Hematology
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CONGRESS NEWS

40th TURKISH ANNUAL HEMATOLOGY CONGRESS

AUTOIMMUNE HEMOLYTIC ANEMIA: CURRENT UNDERSTANDING OF PATHOPHYSIOLOGY

The autoimmune hemolytic anemias (AIHA) constitute a group of uncommon disorders characterized by hemolysis caused by the formation of antibodies (Abs) directed against red cell surface antigens. On the basis of the optimal temperature at which the auto- Abs bind to a patient's erythrocytes in vivo, immune hemolytic anemias are subdivided into 2 major groups: warm-type and cold-type. Cold-type AIHA is further classified into cold agglutinin disease (CAD) and paroxysmal cold hemoglobinuria (PCH). The term primary or idiopathic AIHA is applied when no recognizable underlying disease is present, whereas in secondary AIHA, the anemia is one manifestation of an associated disorder. *Warm-type autoimmune hemolytic anemia* (wAIHA) is the most common form of AIHA. The diagnosis of wAIHA depends on the positivity of direct antiglobulin (coombs) test suggesting that there are RBC coated by antibodies. When circulating through splenic vasculature Ab coated RBCs adhere to macrophages via Fc receptors resulting in phagocytosis of the entire cell or most commonly loss of membrane surface area and formation of spherocytes. In general therapeutic options include suppression of antibody production (steroids, anti CD20) and decrease of RBC destruction (splenectomy). *Cold agglutinin disease (CAD)* is relatively uncommon form of AIHA cases. Cold agglutinin are IgM Abs directed against I red cell antigen which causes RBC agglutination and complement activation. Symptoms due to RBC agglutination include acrocyanosis of the ears, the nose tip, fingers and toes in cold temperature. If blood transfusion is required blood should be warmed to body temperature. Suppression of Ab production by Abs directed against B lymphocytes (anti CD20, rituximab) constitutes the most effective therapy. *Paroxysmal cold hemoglobinuria (PCH)* is mostly diagnosed in children following viral episode with progressive intravascular hemolysis. PCH is caused by a bi-phase hemolysin, an IgG antibody directed against P antigen-first identified by Donath–Landsteiner (DL) in 1904. DL-Ab binds and fixes complement at cold temperature but only after re-warming the Ab dissociates, complement activates and hemolysis occurs. The disease is usually self-limited.

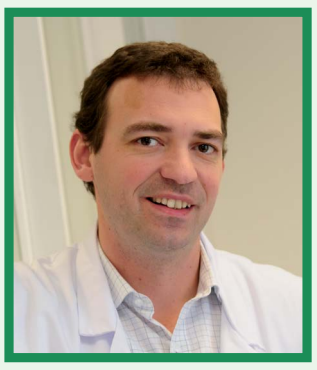
Hannah Tamary MD.
Hematology-Oncology, Schneider Children's Medical Center of Israel, Petach-Tikva, Israel

INHERITED BONE MARROW FAILURE SYNDROMES

The inherited bone marrow (BM) failure syndromes are a diverse group of disorders characterized by BM failure usually in association with one or more extra-haematopoietic abnormality. The BM failure, which can involve all or a single lineage, often presents in childhood but this may not be until adulthood in some cases. Furthermore, some patients initially labeled as "idiopathic aplastic anaemia" are cryptic presentations of these genetic syndromes. Significant advances in the genetics of these syndromes have been made with more than fifty disease genes identified to date. These advances have given insights into normal haematopoiesis and how this is disrupted in patients with BM failure. They have also provided important information on fundamental biological pathways: DNA repair-Fanconi genes; telomere maintenance-dyskeratosis congenita genes; ribosome biogenesis-Shwachman Diamond syndrome and Diamond-Blackfan anaemia genes. Additionally, as these disorders are frequently associated with developmental abnormalities and an increased risk of cancer they are providing insights into human development and the genesis of cancer. In the clinic, genetic tests stemming from the recent advances are facilitating diagnosis and personalized management. Haematopoietic stem cell transplantation using fludarabine based protocols has improved outcomes significantly; management of some of the other complications remains a challenge.

Prof. Inderjeet Dokal
Barts and The London School of Medicine, Queen Mary University of London

UPDATE ON THE DIAGNOSIS AND TREATMENT OF VENOUS THROMBOEMBOISM



The best-known clinical presentations of venous thromboembolism (VTE) are deep vein thrombosis (DVT) of the lower limb and pulmonary embolism (PE). Long-term complications of VTE include recurrent disease, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.

VTE is a cause of substantial morbidity and mortality worldwide. The total incidence of VTE is estimated at 0.7–1.13 per 1,000 per year, and increases with age. PE is the most preventable cause of death in hospitalized patients, and the prevention of VTE is among the top priorities when it comes to improving the quality of healthcare. In 2004, it was estimated that more than 1 million venous thromboembolic events occur each year in France, Germany, Italy, Spain, Sweden and the UK combined, and approximately 12% of all deaths occurring in these six countries were attributable to VTE.

The two-stage treatment of initial heparin therapy overlapping with vitamin K antagonists (VKAs) has been the gold standard for the treatment of VTE in the past half-century. The introduction of LMWHs in the 1980s improved the management of VTE because of their predictable anticoagulant effects without the need for monitoring, allowing shorter hospital stays and outpatient treatment in a substantial portion of patients with VTE. Treatment with LMWHs for 5–10 days, overlapping with and followed by VKAs, is effective but has limitations. VKAs have numerous drug and food interactions, and the parenteral administration of LMWHs may not be practical for every patient. This dual-drug approach is labour- and time-consuming, usurping a lot of healthcare resources. The development of new target-specific oral anticoagulants has the potential to shift the paradigm for the treatment of patients with VTE. This presentation will summarize the clinical studies and available data on the new oral anticoagulants (NOACs) in the treatment of DVT and/or PE, and describes how their use may change/impact on the clinical management of these patients.

Prof. Dr. Peter Verhamme
University of Leuven, Leuven

CURRENT CONCEPTS OF THE BLOOD COAGULATION SYSTEM

Blood coagulation and platelet-dependent primary hemostasis have evolved as important defence mechanisms against bleeding. The systems are carefully controlled by several anticoagulant mechanisms. Disturbances of the natural balance between the pro- and anticoagulant systems caused by genetic or aquired factors may result in bleeding or thrombotic diseases.

Vascular wall damage exposes blood to subendothelial tissues, which triggers the primary haemostasis events. Coordinated interactions between platelet receptors, plasma proteins, and tissue components seal the wounded area. A series of reactions including platelet adhesion, aggregation, release of granule content, and morphological changes generate the platelet plug. The blood coagulation pathway comprises of a series of enzymatic reactions that result in generation of thrombin at sites of the vascular injury. The initiation of the coagulation pathway is triggered exposure of tissue factor (TF) to blood. TF is normally not in contact with blood but abundantly present in cells surrounding the vasculature. (Fig. 1 schematically represents coagulation process).

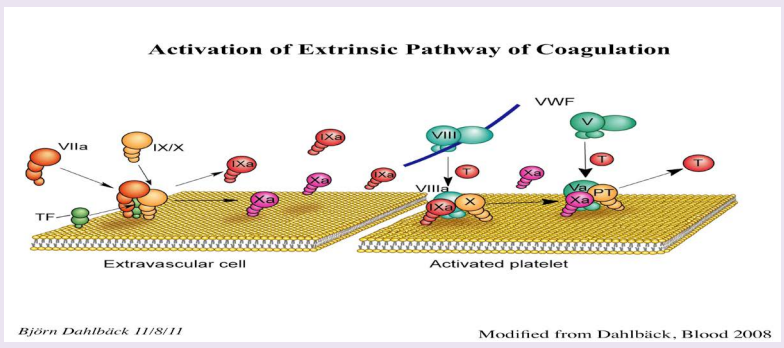


Fig. 1 Activation of coagulation by TF on extravascular cells and propagation on platelets resulting in the generation of thrombin.

Anticoagulant pathways regulating blood coagulation

Blood coagulation is controlled by different anticoagulant mechanisms including enzyme inhibition and degradation of cofactor proteins. Antithrombin (AT) inhibits many of the coagulation enzymes. It is stimulated by heparin and by heparin-like molecules that are present on the surface of endothelial cells. Another mechanism to regulate blood coagulation is mediated by the protein C anticoagulant system (Fig. 2).

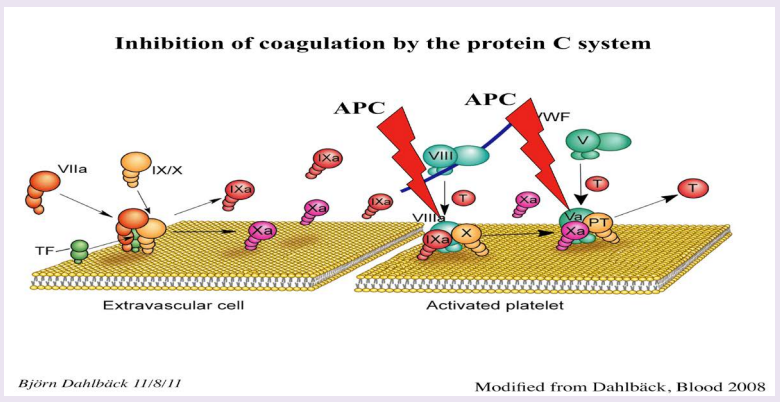


Fig. 2 Points of inhibition of the coagulation system by Activated protein C (APC) (right).

Protein C is activated by thrombin on the surface of intact endothelial cells. Activated protein C (APC) cleaves and inhibits the membrane-bound cofactor protein of coagulation.

Prof. Björn Dahlbäck
Lund University, Department of Laboratory Medicine, Lund University, Malmö, Sweden

TÜRK HEMATOLOJİ DERNEĞİ BİLİMSEL ALT KOMİTE BAŞKANLIK SEÇİM SONUCU

Eritrosit Hastalıkları ve Hemoglobin Bilimsel A.K. Şule ÜNAL
Hematolojide Enfeksiyonlar ve Destek Tedavileri Bilimsel A.K. İrfan YAVAŞOĞLU
Hematopatoloji Bilimsel A.K. Ayşegül ÜNER
Hemofili Bilimsel A.K. Kaan KAVAKLI
Hemostaz-Tromboz Bilimsel A.K. Cengiz BEYAN
Kemik İliği Yetersizliği Bilimsel A.K. Mustafa ÇETİNER
Kök Hücre Nakli Bilimsel A.K. Mutlu ARAT
Kronik Miyelositer Lösemi ve Kronik Miyeloproliferatif Hastalıklar Bilimsel A.K. Burhan TURGUT
Lenfoma Bilimsel A.K. Burhan FERHANOĞLU
Multipl Miyelom Bilimsel A.K. Hayri ÖZSAN
Moleküler Hematoloji ve Sitogenetik Bilimsel A.K. Uğur ÖZBEK

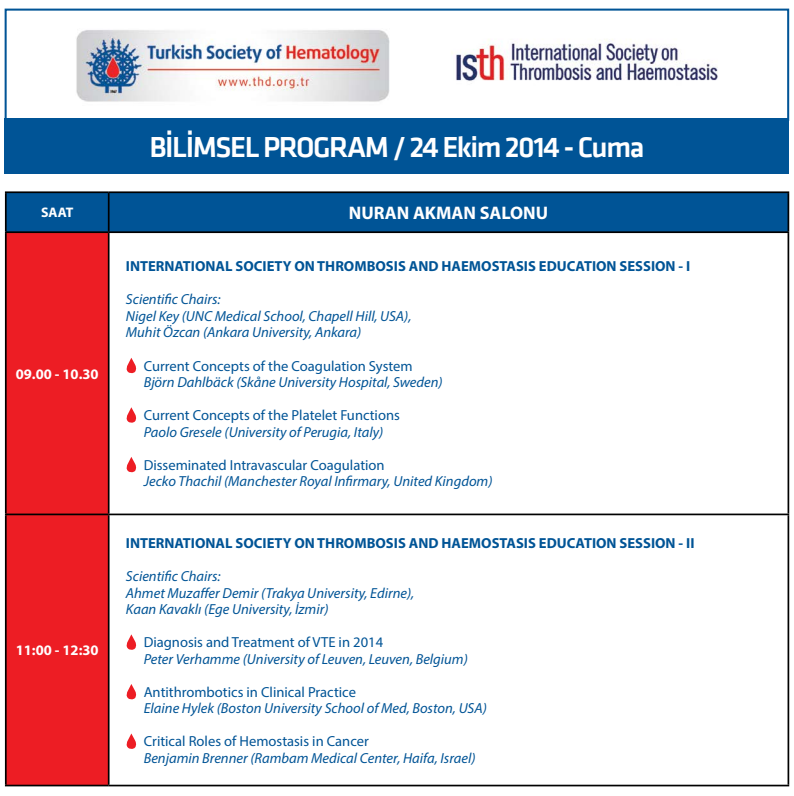
We will be happy to see you at the Turkish Annual Hematology Congress Traditional Award Ceremony and Concert.

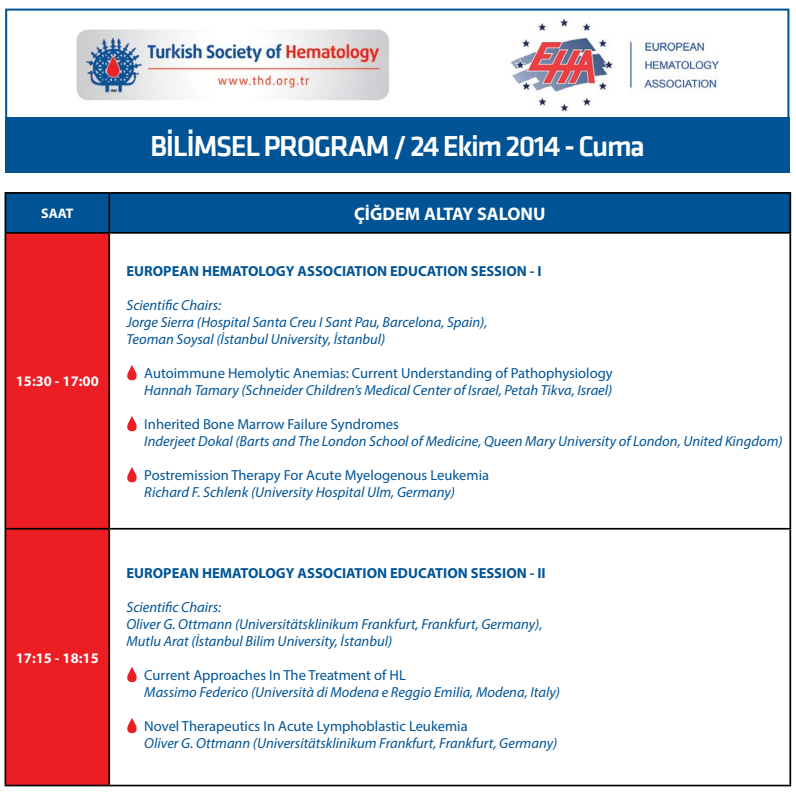
Date : 24 October 2014
Place : Nuran Akman Hall
Time : 21.00 / Award Ceremony
21.30 / Concert

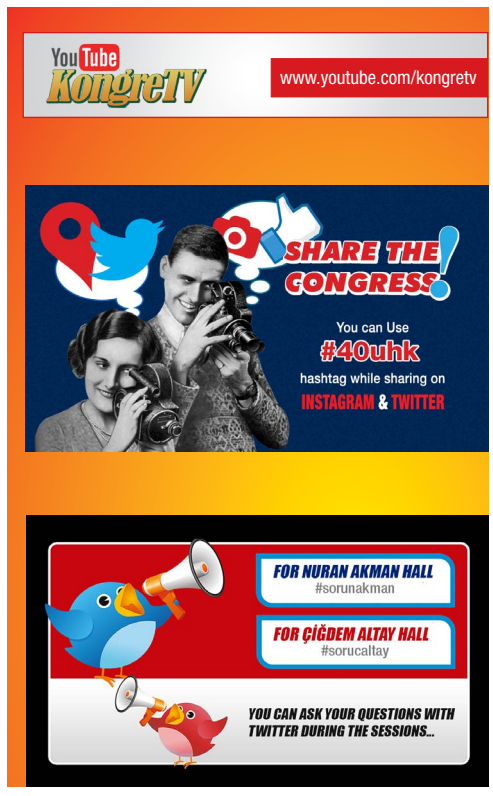
CURRENT CONCEPTS OF THE PLATELET FUNCTIONS

Once considered as little amorphous cytoplasmic fragments, platelets are instead highly structured subcellular elements of 2-3 μm in diameter, that are essential for normal hemostasis but also play important roles in atherosclerosis, inflammation, innate immunity, angiogenesis and tissue repair. 10^{11} platelets are released each day from their bone marrow precursors megakaryocytes to maintain a normal circulating platelet count of 1.5 to 4 x 10^5/μl. Platelets are structured in a complex way containing a plasma membrane, a system of internal membranes (open canalicular and dense tubular systems), a cytoskeleton (microtubules and microfilaments), mitochondria, glycogen granules, storage granules (α-granules and dense granules), lysosomes, and peroxisomes. The plasma membrane has several important functions: it extends inside the platelet through the multiple channels of the surface-connected canalicular system, greatly increasing the platelet surface area and allowing the release of granular materials during platelet secretion; it provides upon platelet activation a procoagulant surface that greatly enhances blood clotting activation; it exposes platelet receptors for activating and inhibiting extracellular messengers. The classical model of platelet plug formation consist in 4 steps: injury, initiation, extension and stabilization. Upon vessel wall damage and the consequent exposure of thrombogenic materials, platelets undergo a highly regulated set of functional responses including adhesion, spreading, release reaction, aggregation and clot retraction. All of these platelet responses function to rapidly form a haemostatic plug that occludes the site of damage to the vascular wall, thus preventing blood loss. The initial crucial step is platelet adhesion to the exposed collagen, a process in which the blood flow shear forces and the interaction between adhesive proteins, collagen and von Willebrand factor, and their receptor on platelets, GPIb/IX/V and GPIa/IIa, play a critical role. Subsequently, platelet activation is started by signaling events that occur downstream of receptors for collagen (GPVI), thrombin (PAR1 and PAR4), adenosine diphosphate (ADP; P2Y1 and P2Y12), and thromboxane A2 (TxA2; TP). Platelet activation produces second messengers needed to raise the cytosolic Ca^{2+} and to lead to the activation of the most abundant platelet receptor $\alpha_{IIb}\beta_3$ (inside-out activation). $\alpha_{IIb}\beta_3$ is a calcium-dependent receptor for fibrinogen, fibronectin, vitronectin, thrombospondin, and von Willebrand factor (vWF), and it is the ultimate responsible of platelet aggregation. Later events in platelet plug formation are those that stabilize the platelet plug and prevent disaggregation, in part by amplifying signaling driven by a number of primers of platelet activation. The final result is a hemostatic plug made of activated platelets embedded within a cross-linked fibrin mesh, a structure stable enough to withstand the shear forces generated by flowing blood in the arterial circulation. An excessive extension of the hemostatic platelet plug formation may lead to an unwanted thrombosis, and to prevent the latter a number of platelet inhibitory mechanisms exist, in part mediated by the vessel wall (i.e. prostacyclin, nitric oxide) and in part by the platelets themselves (i.e. nitric oxide). Finally, to finely tune the platelet response to stimuli, a series of primers of platelet activation, i.e. substances not directly inducing platelet activation but amplifying the platelet response to weak agonists, also participate in platelet plug formation. It is not surprising that alterations that perturb these complex reactions may lead to clinical bleeding, on one side, or to arterial thrombosis, on the other. Besides their central role in hemostasis and in thrombosis, platelets play a role in several other physiologic and/or pathologic phenomena, and first of all in inflammatory reactions. Platelets act as inflammatory cells by responding to a number of typical inflammatory stimuli (cytokines, chemokines, bacterial products, etc.) by migrating into tissue, by releasing several chemokines, inflammatory mediators and enzymes involved in inflammation, and by actively interacting with typical inflammatory cells, primarily with leukocytes. A central role of platelets in the pathogenesis of inflammatory disorders, ranging from allergic asthma, rheumatoid arthritis, inflammatory bowel disease, has been lately demonstrated. Advances in the understanding platelet participation in disease may provide further key insight into the mechanisms of platelet function and may lead to the development of new therapeutic strategies for the treatment of bleeding disorders and of thrombotic conditions but also of inflammatory diseases.

Paolo Gresele
Department of Medicine, Section of Internal and Cardiovascular Medicine, University of Perugia, Perugia, Italy.

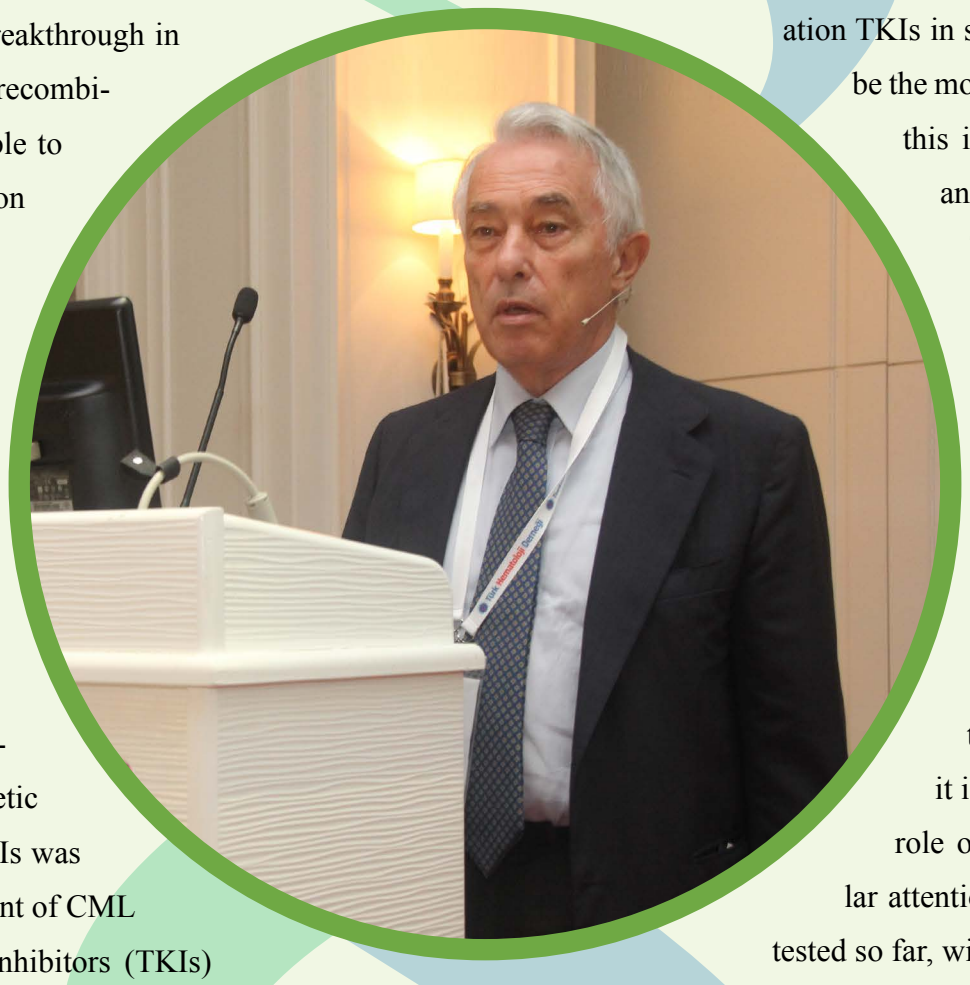






Progress in treatment of CML: from imatinib to ponatinib

The first effective therapy of chronic myeloid leukemia included x-radiation to the spleen and cytotoxic drugs, particularly Busulfan (BUS) and Hydroxyurea (HU). This therapy improved significantly the quality of life during the chronic phase (CP) of the disease, but did neither prevent nor delay the progression to accelerated and blastic phase (AP, BP), with a limited effect on overall survival (OS). The introduction of allogeneic stem cell transplantation (alloSCT) marked the first important advance, because about 50% of the patients who were eligible for alloSCT became Philadelphia–negative, and were cured. Unfortunately, the best success of alloSCT were limited to patients less than 40 years old, while the median age at diagnosis is close to 60 years, and the quality of life after alloSCT was seriously and frequently impaired by the development of a chronic graft-versus-host-disease (CGVHD). The second major breakthrough in therapy was the introduction of human recombinant interferon-alfa (rIFNα), that was able to achieve a complete cytogenetic remission in 15% to 30% of patients, with a significant survival advantage over conventional chemotherapy. However, in few years, at the beginning of this century, all these treatments were rapidly displaced by the discovery of a class of small molecules targeting the tyrosine kinases (TK), particularly the BCR-ABL TK, that causes the leukemic transformation and the leukemic characteristics of Ph+ hematopoietic stem cells. The first in class of these TKIs was Imatinib, that is still the standard treatment of CML for many patients. Rapidly, other TK inhibitors (TKIs) were developed, tested and commercialized, namely Dasatinib, Nilotinib, Bosutinib. and Ponatinib. Not all these compounds are available worldwide, some of them are approved only for second line treatment, and their cost is a problem everywhere. However, they are an extraordinary new class of active agents which we should learn to use to optimize the treatment of CML, not also with the purpose of avoiding death from leukemia, but also of avoiding deaths and complications from treatment, of improving the quality of life, of achieving a cure, as well as of making the better and proper use of the financial resources, that are never unlimited.



Ponatinib is the last drug that was produced, with the aim of overcoming the resistances due to BCR-ABL1 mutations. As a matter of fact, there are no known mutations clearly resistant to ponatinib, and ponatinib is even more active in case of the T315I mutation, that is resistant to all other TKIs. Ponatinib is now approved for second- or third-line treatment, with some differences among countries, and for the treatment of all patients with the T315I mutation. The efficacy of ponatinib in third or fourth line is at least as equal to the efficacy of the other second-generation TKIs in second-line, so that Ponatinib is likely to be the most effective drug in second line. However this is an expectation that must be checked, and hopefully validated, in clinical trials. The main problem of ponatinib is that it inhibits also many other TK, which is a cause of toxicity, particularly of atherosclerotic adverse events with sound clinical consequences. This problem has caused the premature discontinuation of a phase 3 study (EPIC) where ponatinib was tested in first-line vs imatinib. It is to early to discuss the future role of ponatinib in first-line, while it is very important and urgent to define the role of the drug in second-line, with particular attention to the dose. The initial dose that was tested so far, with great efficacy and substantial toxicity, was 45 mg once daily. Several findings suggest that a lower dose will maintain efficacy and decrease toxicity. According to our experience, the best way of using ponatinib may be to titrate the dose to the minimum effective value, based on a monthly evaluation of molecular response. Studies testing this hypothesis will be initiated very soon in Italy, and in other countries.

Michele BACCARANI, MD
Professor of Hematology at the Universities of Chieti, Trieste, Udine and Bologna
Chairman of the CML working parties of European Leukemia Net and of GIMEMA.
Michele.baccarani@unibo.it