launched the EUMDS Registry. In this project, including 19 countries and 150 sites, epidemiological, clinical and lab data on newly diagnosed MDS patients, are collected and analyzed. As of today, 3300 patients have been recruited. In 2012, the Israel MDS group joined the project. We have contributed data on 360 patients, # 4 in the contributors. This project led to more than 100 abstracts in international meetings and 40 publications in first line journals. We will mention some of these studies. de Swart et al. summarized data on the first 1000 patients, validated the IPSS-R prognostic classification, showing its superiority on IPSS (de Swart L. BJH 2015). Another study, focusing on Quality of life (QoL) of LR-MDS patients revealed that these patients suffer from depression, anxiety, pain, discomfort and mobility difficulties, compared to controls (Stauder R, Leukemia 2018) The effects of Erythroid Stimulating Agents (ESAs,) was evaluated: Garelius et al. showed that ESA administration delays RBC transfusion dependency (Garelius HK. J Intern Med 2017). Since in most countries ESA is given to transfusion-dependent MDS patients, it might change the paradigm. Recently, we demonstrated that ESA treatment, is associated with improved outcomes and overall survival (Garelius HK. EHA 2022; submitted). Since prognostic factors are often determined at disease presentation, it was important to develop dynamic parameters. We showed that a rapid decline > 25% in the platelet count within 6 months is an adverse prognostic marker (Itzykson R. Bl Adv 2018) A study focusing on the mutational status was presented at ASH 2021 showing that LR-MDS patients can be grouped into 3 clusters, with a correlation to the clinical status (Malcovati L. ASH 2021) The Israeli group, independently and as a part of the EUMDS, was involved in several projects. Oster et al. suggested a non-invasive calculator to assess the probability of or excluding MDS diagnosis, based on patient characteristics, avoiding BM examination (Oster HS. Bl Adv 2021). We also investigated the correlation between Hb level and QoL. This correlation was found to be partial, and the decrease in QoL was not linear. This suggests that other factors other than Hb might play a role in determining QoL (Haring Y. ASH 2021). We recently presented data on lymphoid aggregates in BM biopsies, suggesting a possible association with poor prognosis (Book-Rabinowitz. Int MDS Symposium, Toronto 2021; submitted). **In summary**, the EUMDS registry is a platform of a scientific project, and an example of international collaboration. Such projects, especially in relatively uncommon diseases, allow collection of enough data to allow meaningful conclusions that might change paradigm and improve patient care. We call all participants of this meeting to join us and improve the quality of this wonderful important project.

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Sp09

EMERGING DATA FOR CANCER ASSOCIATED THROMBOSIS TREATMENT

Piera Sivera

Ospedale Ordine Mauriziano, Torino, Italy

Venous thromboembolism (VTE) is a common complication in patients with malignancies,resulting in deep vein thrombosis, pulmonary embolism and central venous catheter VTE, and is responsible for high morbidity and mortality (1). The prevalence of cancer-associated thrombosis is increasing because of multiple factors, including longer patient survival, anticancer therapies, increased detection of incidental VTE during surveillance imaging, and wider use of central venous catheters. Anticoagulant therapy with low-molecular-weight heparins (LMWHs) was the standard of care for the treatment of cancer-associated thrombosis, with vitamin K antagonists providing a secondary treatment option, until direct oral anticoagulants (DOAC) emerged as alternative first-line treatment options in 2016 (2). Rivaroxaban, Edoxaban and Apixaban are recommended as initial treatment in patients with cancer-associated thrombosis who are not at high risk of gastrointestinal or genitourinary bleeding (3). LMWHs and Fondaparinux are still recommended for prophylaxis of VTE in medically-treated patients with cancer. Rivaroxaban and Apixaban can be used selectively for thromboprophylaxis in patients with malignancies at high risk of VTE, for example in patients with pancreatic cancer or myeloma (4,5). Anticoagulant choice should incorporate a personalised medicine approach that considers cancer type, VTE and bleeding risk factors, drug–drug interactions (DDI), and patient preferences. Patients with cancer often experience narrow therapeutic index polypharmacy and undergo treatment for several simultaneous comorbidities. In this setting the risk of DDI is high in particular during therapy with tyrosine kinase inhibitors (6). Concerns on DDI management include decreased efficacy and bleeding risk. In general, DOAC use is not advisable in combination with drugs that are strong inhibitors of both P-gp and/or CYP3A4 for high bleeding risk and in combination with strong inducers of Pgp and/or CYP3A4 that could markedly reduce DOAC plasma levels. Routine use of plasma level measurements for DOAC, only available in few laboratory centres, is not currently recommended (7). Nevertheless it has recently become increasingly clear that clinicians need to assess the anticoagulant status of a patient receiving anticancer therapies. The global coagulation Test of thrombin generation (TGT) a sensitive method to assess the anticoagulant therapy, provides a global measure of anticoagulant effect by measuring the inhibition of formation of thrombin (FIIa), a common endpoint for both LMWH and FXa inhibitors (8). Furthers studies are warranted to better define the future role of this coagulation test in this subgroup of patients.

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Sp10

VASCULAR DISEASES IN PNH

Hanan Hamed

Professor of Internal medicine and Clinical Hematology Ain Shams University Cairo – Egypt

PNH is a condition in which uncontrolled complement activity leads to systemic complications, principally through intravascular hemolysis and platelet activation. It arises through a somatic mutation of the phosphatidylinositol glycan A (PIG-A)

gene in bone marrow stem cells, 1,2 resulting in disruption to glycosylphosphatidylinositol (GPI) biosynthesis, 3. Among the deficient proteins are the complement regulatory proteinsCD55 andCD59, resulting in increased complement sensitivity of PNH cells, intravascular hemolysis, promotion of inflammatory mediators, and systemic hemoglobin release4 . Patients with PNH can present with multisystemic clinical manifestations due to intravascular hemolysis, thrombosis and bone marrow failure5 . Symptoms are therefore often non-specific, ranging from loss of vision (due to retinal thrombosis), headache and nausea/vomiting (due to cerebral thrombosis), pulmonary hypertension (due to pulmonary embolism), anaemia, through to pain and swelling in the lower extremities (due to deep vein thrombosis), renal failure and other symptoms affecting different systems6 . Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of deaths of which the cause is known. Further, 29% to 44% of patients with PNH have been reported to have at least 1 thromboembolic event during the course of their disease, although the reason(s) a thrombotic event may suddenly occur remains an enigma7,8,9. Platelet activation, complementmediated hemolysis, impaired nitric oxide (NO) bioavailability, impairment of the fibrinolytic system, and inflammatory mediators are all proposed mechanisms and thought to be responsible for the increased thrombotic risk in patients with PNH. Multiple factors are likely to contribute to any one thrombotic event in patients with PNH. 10 Therapeutic strategies include terminal complement blockade and bone marrow transplantation. Eculizumab, a monoclonal antibody complement inhibitor, is highly effective and the only licensed therapy for PNH.11 The therapeutic anti-C5 antibody eculizumab (Soliris, Alexion) has proven effective in controlling intravascular hemolysis in vivo, leading to remarkable clinical benefit in a majority of PNH patients.12,13 Yet, persistent C3 activation occurring during eculizumab treatment may lead to progressive deposition of C3 fragments on affected erythrocytes and subsequent C3-mediated extravascular hemolysis, possibly limiting the hematologic benefit of anti-C5 treatment.14,15 Thus, upstream inhibition of the complement cascade seems an appropriate strategy to improve the results of current complement-targeted treatment.16,17

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Sp11

HOW WE (WILL) TREAT PNH?

Semra AYDIN

Department of Oncology, Hematology, Immuno-Oncology and Rheumatology, University Hospital of Bonn, Bonn, Germany

Clinical signs arising from intravascular hemolysis, hemolysis-related transfusions and thrombosis are indications for treatment initiation in paroxysmal nocturnal hemoglobinuria (PNH), whereas clone size *per se* is not. Eculizumab prevents intravascular hemolysis and reduces significantly thromboembolic risk resulting in a five-year overall survival of >90%. Hemoglobin value, LDH and reticulocyte count are used to define treatment response. Residual intravascular hemolysis is mainly caused by an incomplete C5 blockage and can lead to continuous low–grade hemolysis or transient breakthrough hemolysis episodes in 10-15% of PNH patients. Additional complement–amplifying conditions such as infections, surgery or pregnancy may overcome efficient therapeutic levels of Eculizumab and therefore require dose adjustments. *C3–mediated extra–vascular hemolysis* represents the main reason for residual anemia during anti–C5 treatment. Patients with an inherited C5-variant lack response to Eculizumab and have been directed (in past) towards allogeneic HSCT. Transplantation has an overall mortality of up to 30%, with a higher risk in patients with previous thrombosis. A plethora of novel therapeutic agents are reported to impact on both; residual intravascular hemolysis and C3–mediated extra–vascular hemolysis. The new C5 inhibitor Ravalizumab with an eight–week i.v. dosing interval showed non-inferiority to Eculizumab. Crovalimab, binding on the single missense C5 heterozygous mutation is injected s.c. monthly; two large phase III trials are ongoing as add on- and mono-therapy. Others, such as Pozelimab, injected subcutaneously on a weekly basis after an initial IV loading dose or Tesidolumab are still under current investigation. Currently investigated proximal inhibitors are acting towards: (i) the C3 complement; (ii) complement factor D or (iii) the complement factor B. They are aiming in particular to prevent C3–mediated extra–vascular hemolysis. Pegcetacoplan is a PEGylated version of compstatin which binds to C3 and is injected s.c. in monotherapy 4 weeks after initial concomitant therapy with Eculizumab. In a recent phase III trial, pegcetacoplan showed superiority to eculizumab in hemoglobin change from baseline and is now approved by the FDA for patients with PNH who are either treatment–naive or switching from anti–C5 monoclonal antibodies. Danicopan is an oral first–in–class factor D complement alternative pathway inhibitor and decreased significantly transfusion requirement, as shown in a phase II trial (phase III ongoing). BCX9930, another FD inhibitor in early development is given orally and demonstrated initial clinical efficacy both as add–on therapy in patients with inadequate response to eculizumab as well as in monotherapy in treatment–naive patients. In conclusion, novel proximal and distal complement inhibitors with different application modalities, in part as add-on or monotherapy seem to improve significantly intra- and extra–vascular hemolysis in PNH, resulting in a better hematological benefit. Before choosing specific treatment, hematologists have to assess hemolysis, thrombosis and patients‘ bone marrow function. Future studies will help to explore long-term efficacy and safety of these novel agents.

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Sp12

THE THEN, NOW, & FUTURE OF ENGINEERED T-CELL THERAPEUTICS FOR HUMAN APPLICATION

Bruce Levine, Ph.D.

The University of Pennsylvania, Philadelphia, PA