HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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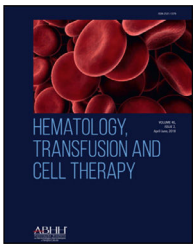

SPEAKER PRESENTATIONS

Sp 15

CURRENT THERAPY FOR INDOLENT LYMPHOMAS

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Introduction

Indolent lymphomas are mature B-cell neoplasms with a tendency of slow progression and a possible period of observation without treatment. It's a group of heterogeneous diseases, with a less aggressive presentation when compare with other lymphomas, but with frequent relapses and consider incurable. This group contains follicular lymphoma, lymphoplasmacytic lymphoma and marginal zone lymphoma.

Follicular lymphoma (FL)

FL is the most common indolent lymphoma and the second in prevalence between non-Hodgkin`s lymphomas (NHL)[1]. About 20% of patients will progress within 2 years of first line treatment and have worse prognosis (POD24). This group has a markedly reduced overall survival (OS) (around 50% in 5 years), enriched by transformations to aggressive lymphomas. On the other hand, close to 30% of patients in need of therapy can be treated only with anti-CD20 monotherapy, highlighting the great heterogeneous of this disease. Albeit several prognosis factors and risk classification, how to best separate those different FL patients at diagnosis remains unclear. Generally, options for first-line treatment are based in chemotherapy (Bendamustine or CHOP/CVP) with anti-CD20 immunotherapy (Rituximab or Obinutuzumab). There are data supporting Bendamustine plus rituximab (BR) for grade I/II FL, but with no gain in OS in long term studies when compared to other chemotherapy regimens[2]. The same with anti-CD20, where although better progression-free survival (PFS) versus rituximab, obinutuzumab had no gain in OS[3]. After completing 6 cycles, it's common to offer the anti-CD20 used previously as maintenance therapy for 2 years (every other month). This is also a stablished practice, based in long term study with sustained PFS advantage, including reducing risk of transformation into aggressive lymphoma. However, since there is no OS benefit, it's still considered optional. Lenalidomide plus Rituximab ("R^2"), in untreated FL, had an equal PFS rate at 3 years compared with Rituximab plus Chemotherapy, with less hematological toxicity and neutropenic fever, but with no long follow-up data yet. The combination was also effective in the relapse setting, with a median of 40 months in PFS, and it is considered for patients unfit for intensive regimens with autologous transplant as consolidation. Chimeric antigen receptor-modified T cells (CAR-T) against CD19 is becoming widely use in lymphoma and has showed efficacy in relapse/refractory FL patients, with report of high complete remission rate and sustained remissions.

Lymphoplasmacytic lymphoma (LPL)

LPL is a lymphoma where lymphoplasmacytic cells infiltrates the bone marrow and lymph nodes and produces monoclonal protein. Almost always it is of IgM subtype, and it's called Waldenström macroglobulinemia (WM). The *MYD88* L265P mutation occurs in over 90% of cases and has a diagnostic and prognostic role, but it's not specific of WM. *CXCR4* mutation is present in about 30% of patients and is associated with symptomatic disease, higher IgM levels and bone marrow involvement. WM is a disease of elderly patients. Treatment should be delayed until symptoms occur or cytopenias related to the disease[4]. Patients with low tumor burden, frail and where treatment isn't urgent, the combination of dexamethasone, cyclophosphamide and rituximab (DRC) is a well-tolerate and unexpensive option. The change of cyclophosphamide for bortezomib (BDR) is also a good first-line

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option, especially for patients with cytopenias and no neuropathy. BR is an effective chemotherapy regimen for WM, but myelotoxicity can be an issue in already cytopenic patients. Ibrutinib with or without rituximab can be used in first line or relapsed patients, but it seems to have a worse response in patients with wild type *MYD88*. Acalabrutinib and Venetoclax are other new options with response in relapsed setting, including in patient's refractory to ibrutinib. Zanubritinib, a new BTK inhibitor for WM treatment, is at least as effective as ibrutinib with perhaps a better toxicity profile.

Marginal Zone B-cell lymphomas (MZL)

The marginal zone B-cell lymphomas (MZLs) comprise extra nodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), splenic MZL (SMZL) with or without villous lymphocytes and nodal MZL (NMZL) with or without monocytoid B cells. These are three distinct clinical entities with specific diagnostic criteria, clinical and therapeutic implications.

Regarding to localize H. pylori-positive gastric MZL, the initial treatment should be H. pylori eradication. This treatment can induce lymphoma regression and long-term clinical disease control in the most of 50% of the patients. In patients who do not achieve lymphoma regression following antibiotic therapy, and the rare ones not associated with H. pylori infections, radiotherapy seems to be the best choice (considering localized disease). Patients who require systemic treatment are not very common, but long-term data from the randomized study IELGS-19 showed better response rates and event-free survival when adding rituximab to chlorambucil, but no OS gain compared to chlorambucil alone[5]. SMZL in asymptomatic patients should be observed. There are no randomize trials, but when treatment is required, splenectomy and rituximab monotherapy are considered first-line. For asymptomatic patient diagnosed with NMZL is also recommended only observation. If systemic treatment is indicated, chemo-immunotherapy can be performed.

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Sp 16

ELN recommendations for treating MDS

David Bowen

Whilst peer-reviewed published guidelines have appropriate scrutiny and endorsement to support their validity, the reality is that these often become at least partially outdated soon after publication. In developing the latest iteration of guidelines for the diagnosis and management of MDS, the European LeukemiaNet MDS guideline group, has sought to create a web-based interface that is interactive, portable, and capable of dynamic updating at least annually. The guideline development process involved systematic literature review, expert opinion, and scenario analysis. The faculty was diverse; from 18 European countries. The group included Junior Faculty who fed back on content and the practicality for access from mobile devices. The final product is interactive and iterative, with upfront 'headline' recommendations supported by expanded information pages for readers requiring further detail [https://mds-europe.org/]. Examples of updates from our previous ELN guidance are:

Diagnosis: we suggest mutation analysis in all patients where available, to inform prognosis and management. We explain the strengths and the limitations of current knowledge, including discussion of the clonal cytopenias. We also include consideration of germline predisposition syndromes.

Prognosis: we provide calculation tools for IPSS-R and will update this with the forthcoming IPSS-Mol during late 2021/2022.

Low-risk MDS: we describe new data for iron chelation, for early use of Erythropoietic Stimulating Agents and for novel agents such as Luspatercept. Pathways for use of these agents are presented.

High-risk MDS: recommendations are given for the use of hypomethylating agents, chemotherapy, and allogeneic stem cell transplant. An interactive stem cell transplant algorithm including comorbidity is available to guide transplant decisions.

This project was supported by Horizon 2020 funding under the auspices of the MDS-RIGHT programme. The guidelines have recently been endorsed by the European Haematology Association. Discussions are ongoing with international colleagues such that the website may accommodate international variation of recommendations.

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Sp 17

How I treat Polycythemia vera

Barbara Mora, Frencesco Passamonti

Polycythemia vera (PV) is a Philadelphia-negative myeloproliferative neoplasms (MPNs),[1] characterized by high myeloid cells production secondary to mutations in Janus kinase 2 (JAK2) gene. [2,3] Incidence rate is higher in advanced age. [4]

Clinical phenotype is dominated by systemic symptoms, pruritus and microvascular disturbances; splenomegaly may be detected in 30-40% of cases. [5] In the long term, what impacts on outcome is the increased risk of thrombosis, evolution into post-PV myelofibrosis (PPV-MF), or into blast phase (BP). [6]

The main aim of PV treatment is preventing vascular events. [7,8] Patients are defined at high risk (HR) if they are older than 60 years or had a previous thrombosis, [7,8] but leukocytosis and high JAK2 allele burden might be of value. [9] Standard therapy for all PV patients includes phlebotomies, to maintain the hematocrit (Hct) below 45%, and aspirin. [10,11] For HR patients, cytoreduction must be added. [12] Therapy could also be started in case of signs of hyper-myeloproliferation (progressive leukocytosis, excessive thrombocytosis, splenomegaly), uncontrolled symptoms or intolerance to phlebotomies. [7,8] Hydroxyurea (HU) is the first choice in most countries since conventional interferons (IFNs) are burdened by numerous side effects. [13]

Pegylated forms (peg-IFNs) have been developed to improve tolerability through less frequent administrations. [14] Two recent phase 3 trials have investigated the potential benefits of first line peg-IFNs in HR PV patients. [15,16] The MPD-RC 112 study compared peg-IFN α-2a with HU. [15] At 24 months, peg-IFN was associated to a higher ORR (59.6%) compared to HU (40.7%). [15] The PROUD PV phase 3 trial was a randomized non-inferiority study between ropeg-IFN α-2b and HU. [16] The primary endpoint was composite: obtaining a complete hematologic response (CHR) and a normal spleen volume. [16] Given that few patients had baseline splenomegaly, the non-inferiority of ropeg-IFN was not apparent at 12 months. [16] The extension phase was named CONTINUATION PV. [16] At 36 months, the ropeg-IFN cohort obtained a significantly higher percentage of CHR with improved disease burden (52.6%) in comparison with the HU-treated one (37.8%). [16] Besides, continuing ropeg-IFN beyond one year was associated with sustained molecular response. [16] We suggest considering IFNs in young patients, fertile females, subjects without relevant vascular risk factors or massive splenomegaly.

About 15% of PV patients develops resistance/intolerance to HU. [17] The choice of a second line therapy should be based on patient's age and preferences, in addition to the current evidence on alternative treatments. [7,8] To date, the JAK1/2 inhibitor Ruxolitinib (RUX) and IFNs are the available options. Two prospective randomized studies, named RESPONSE [18,19] and RESPONSE-2 [20-22] evaluated PV patients resistant/intolerant to HU and in need of phlebotomy, with (RESPONSE) or without (RESPONSE-2) splenomegaly. [18-22] Primary composite endpoints were Hct control in the absence of phlebotomy (both studies) and 35% reduction in spleen volume (SVR) at week 32 (only for RESPONSE). [18-22] In the RESPONSE trial, the primary composite endpoint was achieved in 21% of patients in the RUX cohort vs. 1% on BAT. [18] Hct control was reached in 60% with RUX vs. 20% with BAT; SVR35 in 38% vs. 1% of patients. [18] A CHR was more frequently achieved with RUX (24% vs. 9%). [18] At five years, the probability of maintaining primary composite endpoint and CHR were 74% and 55%, respectively. [19] The five-years OS was comparable between arms (around 91%), but this analysis did not account for the extensive crossover. [19] The RESPONSE-2 study evaluated a "more conventional" PV population. [20-22] Hct control was reached in 62.2% of the RUX arm compared to 18.7% on BAT. [20] At week 80 and 260, the median duration of Hct control on RUX was 78% and not reached, respectively. [21,22] To note, in both studies the incidence of vascular events was lower in the RUX arm when compared to BAT arm. [19;22] In RUX treated patients we registered an high incidence of non-melanoma skin cancers (NMSC), [19,22], confirmed on a cohort of 151 RUX-treated secondary myelofibrosis. [24] The phase 2 MPD-RC 111 trial evaluated peg-IFN α-2a in 50 HR PV patients, resistant/intolerant to HU. [25] At 12 months, ORR and CR were 60% and 22%, respectively. [25] We find these results inferior compared to other trials on IFNs, probably because of the unfavorable features of the study population. [17] Thrombotic events occurred respectively in 2% and 5% of patients at one and two years, but the median follow up was only of 19.6 months. [25] We think that, based on the five-years follow-up, RUX appears to be effective as second line therapy, particularly in improving Hct or splenomegaly with a good control of thrombotic events.

Concerning low risk population, an interim analysis of the phase 2 randomized clinical trial LOW-PV, comparing standard therapy to the addition of ropeg-IFN α-2b in LR cases, has recently been published. [26] The primary composite endpoint of maintaining a Hct lower or equal to 45% for 12 months, without evidence of disease progression was reached in 84% of ropeg-IFN α-2b vs. 60% of standard treated patients. [26] Additionally, ropeg-IFN was associated with a reduction in phlebotomies need, symptoms burden and leuko-thrombocytosis. [28] Even though Hct control is often used as a surrogate of reduced thrombosis risk, we think that follow-up is presently too short to prove a protective vascular effect of ropeg-IFN α-2b in LR patients.

To date, there is little evidence that any of the available treatments might delay transformation into PPV-MF, which is associated with a substantial OS reduction. [27] An early detection of evolution into PPV-MF is therefore fundamental for optimizing treatment, especially for patients eligible to allogenic hematopoietic stem cells transplant (allo-HSCT). [7,8] Therefore, it is essential to carefully monitor patients for possible signs of transformation, as the development of anemia or splenomegaly. [28] Female patients seems to have a slower time to progression [29]. If PPV-MF is suspected, it is essential to perform a bone marrow evaluation and cytogenetic studies, since they have prognostic relevance. [30,31] PPV-MF survival is defined by the recently developed MYSEC-PM (MYelofibrosis SECondary to polycythemia vera and essential thrombocythemia-prognostic model). [32,33]. For patients below 70 years and in the higher MYSEC-PM categories, allo-HSCT outcome could be predicted by the MTSS (Myelofibrosis Transplant Scoring System) model. [34] The allocation of PPV-MF patients to allo-HSCT is therefore personalized. [35]

Future studies on PV treatment should focus on the pathogenesis of the disease and on possible pathways of progression, to prevent this unfavorable evolution. Special focus must be on familial cases of PV. [36]

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NURSING PRESENTATIONS

Sp 18

Haematological emergencies and the early warning score tool for nurses

Dana Parness

This talk will focus on major hematological emergencies, and the nurse's role in recognizing the red flags, responding acutely and treating, while educating the next generation

I will discuss three main hematological emergencies using real life clinical cases, to review the relevant classification scores, risk factors, and treatment approach- enabling better understanding of the nurse's role in early diagnosis and treatment

TLS-tumor lysis syndrome- Recognizing patients at risk for TLS, and monitoring them for early signs of TLS, while applying prevention strategies, such as Allopurinol and hydration for high-risk patients. Using the Cairo Bishop classification score for definite diagnosis, using clinical and laboratory data. We will further discuss, how to best monitor and treat patients with established TLS, as recommended by the latest guidelines, through the different clinical cases presented.

SVCS- superior vena cava syndrome

We will discuss the myriad of symptoms and signs pointing to SVC syndrome, the different risk factors, and etiologies, as well as the differential diagnosis and approach to establishing a definite diagnosis. As abovementioned, using clinical cases we will discuss the updated approach to diagnosis and treatment, focusing on the nurse's crucial role in prevention and early response and management

Neutropenia fever-sepsis

Viewing this crucial subject in treating hematological patients, we will discuss in depth the definitions of neutropenia, and the different scores used to delineate sepsis, septic shock and severe shock. We will then continue to case studies, exploring the approach, to the febrile neutropenic patient- starting from the basic management, eg hemodynamic monitoring, fluid resuscitation, laboratory workup. Thereafter, we will continue to practice early signs of sepsis and grades of shock, then covering in brief the diagnostic possibilities and various treatment regimens available, by clinical, laboratory and imaging studies, stressing the importance of thorough physical exam, blood cultures, early initiation of broad-spectrum antibiotics, and adequate fluid balance. To summarize this subject, we will discuss different strategies for prevention of sepsis, and the crucial role of the nurse team in diagnosing, treating and preventing complications

We will close the meeting, with a summary of the abovementioned subjects, emphasizing the importance of the nurse's role in every patient case- whether by frequent monitoring, attention to subtle changes or by creating close and trusting relationships with the patients and their caregivers, all of which enable early recognition and intervention, crucial to the lives of our patients.

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Sp 19

How to COVID pandemic changed clinical practice

Medine Yılmaz

The corona virus disease (COVID) 19 pandemic has affected the entire health system and the delivery of health services. This influence has brought about the change in clinical practices. Nurses are essential in the fight against the patient care, COVID 19. The management of COVID 19 has shown some differences according to the countries' health systems and health manpower. In this context, this presentation talk will focus on the reflections of the COVID 19 pandemic on clinical practices in Turkey.

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PEDIATRIC PRESENTATIONS

Sp 09

Congenital neutropenias: Türkish Registry

Deniz Yılmaz Karapınar

Severe congenital neutropenia is a rare disease, and autosomal dominantly inherited. ELANE mutation is the most frequently observed genetic defect in the registries from North America and Western Europe. However, in eastern countries where consanguineous marriages are common, autosomal recessive forms might be more frequent.

Two hundred and sixteen patients with severe congenital neutropenia from 28 different pediatric centers in Turkey were registered. Patients inclusion and exclusion strategies apre shown in Figure-1.

The most frequently observed mutation was HAX1 mutation (n = 78, 36.1%). A heterozygous ELANE mutation was detected in 29 patients (13.4%) in our cohort. Biallelic mutations of G6PC3 (n = 9, 4.3%), CSF3R (n = 6, 2.9%), and JAGN1 (n = 2, 1%) were also observed (Table 1). Eighty seven percent of HAX1 mutations were detected in the same point of p.

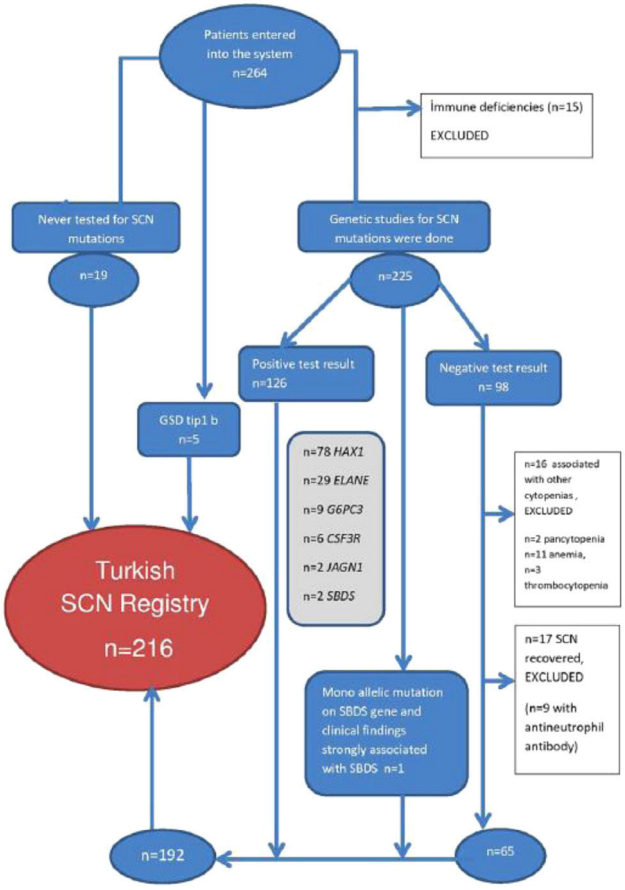
Table 1 – Congenital Neutropenia mutations and their frequencies in the Turkish Severe Congenital Neutropenia Registry

Mutation analyses	n(%)
HAX1 (+)	78(36.1)
ELANE (+)	29(13.4)
G6PC3 (+)	9(4.2)
CSF3R (+)	6(2.8)
JAGN1 (+)	2(1)
ELANE-/HAX1-	23(10.6)
ELANE-/HAX1-/G6PC3-	20(9.3)
ELANE-/HAX1-/G6PC3-/JAGN1-/CSF3R-	22(10.2)
GSDtype 1b	5(2.3)
SBDS	3(1.4)
No genetic testing performed	19 (8.8)

W44X. There were 6 patients who had a HAX1 mutation other than c.130-131 pW44X point mutation. Four had novel mutations. The novel mutations were detected in 7 ELANE patients. Interestingly 2 out of 4 patients with CSF3R mutation and 4 out of 9 patients with G6PC3 had a novel mutation.

Granulocyte colony-stimulating factor treatment was given to 174 patients (80.6%). Two patients died with infectious complications, and five patients developed myelodysplastic syndrome/acute myeloblastic leukemia (Table 2). The mean (± mean standard error) follow-up period was 129.7 ± 76.3 months, and overall survival was 96.8% (CI, 94.4-99.1%) at the age of 15 years.

In Turkey, mutation analysis should be started with HAX1, and if this is negative, ELANE and G6PC3 should be checked. Because of the very high percentage of consanguineous marriage, rare mutations should be tested in patients with a negative mutation screen.



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Sp 10

Hereditary macrothrombocyte disorders

Zühre Kaya

Hereditary macrothrombocyte disorders as known inherited macrothrombocytopenia (IMTP) are gaining greater recognition through advanced genetic and molecular studies. It is a heterogenous group of rare bleeding disorders characterized by abnormally giant platelets, thrombocytopenia, mild to moderate bleeding phenotypes, and/or positive family history and/or syndromic findings. The main characteristic features of macrothrombocytopenia are reduced platelet count (<150,000/μL) and significantly enlarged platelets (mean platelet volume (MPV) >12fL). Up to now, more than 30 genes linked to IMTP have been identified in nearly half of the patients with syndromic and non-syndromic IMTP. All inheritance patterns, including autosomal dominant, recessive, and sex-linked, have been described; however, nearly 50% of affected patients have unidentified genetic mutations or molecular abnormalities. The early and late stages of megakaryopoiesis and subsequent proplatelet formation and functional platelet are regulated by a large number of genes. Defects in these genes result in the dysfunction of several steps in megakaryopoiesis, proplatelet formation, and mature platelet. Many patients with non-syndromic IMTP are either asymptomatic or have minor bleeding manifestations and, detected incidentally with platelet count and morphology evaluation; however, patients with syndromic IMTP may be early diagnosed by specific clinical findings in addition to macrothrombocytopenia. Physicians should suspect IMTP if the following clinical and laboratory findings are present:

a Hearing loss, cataracts, impaired renal function, elevated hepatic enzymes and Döhle-like bodies in neutrophil for non-muscle myosin heavy chain (MYH)-9 related disease,
b Splenomegaly, bone marrow fibrosis, pale platelet and elevated serum levels of vitamin B12 for gray platelet syndrome,
c Cardiac abnormalities, dysmorphic face, digital abnormalities and mental retardation for Paris Trousseau thrombocytopenia/Jacobsen syndrome,
d Craniofacial defects, cardiac abnormalities, mental retardation, hypotonia, thymic aplasia, immune deficiency for DiGeorge syndrome/Velocardiofacial syndrome,
e Xanthomas, premature atherosclerosis, arthritis, hemolytic anemia with stomatocytes, elevated plasma phytosterols for sitosterolemia.

No definitive guidelines are available for managing asymptomatic or mildly symptomatic patients with IMTP; however, platelet transfusion, antifibrinolytic therapy, and recombinant factor VIIa are usually recommended for those with severe bleeding manifestations or prior to surgery. Recently, it has been reported that thrombopoietin-receptor agonists can be used in some patients with MYH9 related disorders. The International Society of Thrombosis and Haemostasis' scientific subcommittee on platelet physiology has published guidelines for diagnosing IMTP. In this approach, personal and family history, and physical examination are the key, followed by i) investigation of platelet count and morphology, ii) evaluation of platelet function by light transmission aggregometry, and iii) a panel of tests to assess granule contents and platelet surface markers by electron microscopy and flow cytometry studies. Further, next-generation sequencing has greatly expanded the molecular repertoire of IMTP, thus enabling the identification of new disorders.

Laboratory findings[2,5,14,15]

a Abnormal complete blood count parameters, including platelet count and MPV may be detected incidentally in many cases. Platelet count below 150,000/μL and significantly increased platelet size (MPV >12 fL) are pathognomonic findings.
b Abnormal platelet morphology may be observed in peripheral blood smear. In patients with IMTP, on average, 20% of platelets are large (>4μm diameter), and 12% are giant (>8 μm diameter) (normal platelets size are between 1.5 μm and 3 μm in diameter). As well, *vacuolated platelets* for GATA1 related disease, *giant platelets* for MYH9 related disease, biallelic Bernard Soulier syndrome (BSS) (GP1bα, GP1bβ and GP9-moderate to severe phenotype), GPS, FLNA related and TUBB1 related disease, *large platelet* for monoallelic BSS (GP1bα-mild phenotype), Paris-Trousseau/ Jacobsen syndrome, GATA1 related-, ITGA2B- and ITGB3 related-disorders are diagnostic signs in peripheral blood smear.
c Abnormal platelet function by light transmission aggregometry may be observed in patients with BSS (*e.g.*, Ristosetin induced platelet aggregation response is absent).
d Immunofluorescence testing with antibody against nonmuscle myosin heavy chain reveals a spotty abnormal distribution of these molecules in patients with MYH9 disorders.
e Flow cytometry reveals lack of GP1bα, GP1bβ and GP IX receptor in patients with BSS.
f Two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the surface radio iodinated platelet glycoproteins results show the absence of GPIb which identifies BSS.
g Electron microscopy reveals abnormal ultrastructure of platelets (*e.g.*, lack of alpha granules and inclusions in MYH9 disorders, giant fused alpha granules in Paris-Trousseau syndrome).
h The next-generation sequencing technology has enabled comprehensive genetic testing using broad diagnostic panels for IMTP related disorders. Recent studies using whole-exome sequencing and whole-genome sequencing have greatly contributed to the early recognition of IMTP related genes and the detection of pathogenic variants within these genes.

v. Treatment: No definitive guidelines are available for managing asymptomatic or mildly symptomatic patients with IMTP; however, platelet transfusion, antifibrinolytic therapy, and recombinant FVIIa are usually recommended for those with severe bleeding manifestations.[5,15] Recently, it has been reported that TPO-receptor agonists can be used in some patients with MYH9 related disorders.[5]

Conclusion: The International Society of Thrombosis and Haemostasis' scientific subcommittee on platelet physiology has published guidelines for diagnosing IMTP. In this approach, personal and family history, and physical examination are the key, followed by *i*) investigation of platelet count and morphology, *ii*) evaluation of platelet function by light transmission aggregometry, and *iii*) a panel of tests to assess granule contents and platelet surface markers by electron microscopy and flow cytometry studies. Further, next-generation sequencing has greatly expanded the molecular repertoire of IMTP, thus enabling the identification of new disorders.

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Sp 11

Treatment of sickle cell in 2021

Salam Alkindi

Sickle cell disease (SCD) is an inherited disorder prevalent in many areas of the world including Africa, Middle East and parts of India. It is characterized by repetitive episodes of vaso- occlusive (VOC) process leading to recurrent painful episodes, hemolytic anemia, and predisposition to infection. Sickle cell manifestations varies and it includes VOC leading to recurrent painful episodes, or organ specific complications such as acute chest syndrome, stroke, splenic sequestration, and many skeletal complications. Although the prognosis of patients with SCD has improved, due to introduction of vaccination, use of antibiotics prophylaxis and blood transfusions, however still patients are dying prematurely. Better understanding of pathophysiology of the disease as well as worldwide interest in the disease has allowed more progress on preventing these complications and development of more focused pharmacological therapies. Hemoglobin polymerization is a primary triggering event in the pathophysiology of the disease, leading to the sickling process, this usually ignite an inflammatory process/ tissue ischemia and increased adhesions. This understanding of the pathophysiology has allowed scientist to develop drugs (three FDA approved within 2 years) that interfere with these processes such as Voxelotor & Hydroxyurea (interfere with polymerization), L-glutamine and Omega 3 (interfere with inflammatory process and oxidative stress) and Crizanluzimab and Tinzaparin (works by inhibiting adhesion molecules). The availability of these therapeutic interventions will allow patients and physicians the freedom to have patient specific therapeutic interventions including development of combinations protocols. SCD is very complex and this meant that drug with multi-faceted action such as Hydroxyurea will remain with us for some time. Further progress also made in the area of bone marrow transplant (including alternative donor pool) and gene therapy /gene editing.

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