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MYELOPROLIFERATIVE NEOPLASMS: SCIENTIFIC ADVANCEMENTS AND IMPACT ON CLINICAL PRACTICE

Report from the 16th International Hematology Expert Meeting (IHEM)
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Preface

Dear colleagues,

the 16th International Hematology Expert Meeting (IHEM®), organized by CEMPO as a hybrid meeting May 11 to 13, 2023 in Malága, Spain, drew over 500 participants from 20 countries who had the opportunity to listen to many stimulating talks on latest updates and new perspectives in the management of myeloproliferative neoplasms (MPNs).

Patients affected by MPNs face long, chronic, slowly deteriorating diseases that require effective and safe life-long therapy concepts offering a good quality of life at the same time. The introduction of pegylated interferons for MPN treatment was a major step forward concerning tolerability compared to non-pegylated interferons, and today these agents are continuously gaining importance due to an evolved understanding of their disease-modifying potential.

This report summarizes talks presented at IHEM 2023 focusing on the pathogenesis of MPNs, treatment options and challenging clinical cases as well as the patient perspective.

Heinz Gisslinger, MD
Chair of scientific committee,
Chair of CEMPO

CEMPO
Central European Myeloproliferative Neoplasms Organisation

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Pathogenesis of Myeloproliferative Neoplasms (MPN)

Clonal hematopoiesis of indeterminate potential (CHIP)

(Prof. Radek Skoda, University Basel, Switzerland)

CHIP involves the presence of somatic mutations of myeloid malignancy-associated genes in blood or bone marrow without evidence of hematological malignancy [1]. The *JAK2* gene is among the most frequently mutated genes in CHIP, with the V617F mutation being the driver for most MPN. In the general population, the prevalence of *JAK2*-V617F (mostly with a variant allele fraction [VAF] <1%) is about 30-fold higher than the prevalence of diagnosed *JAK2*V617F-positive MPN [2].

The *JAK2*V617F mutation is often acquired several decades before the diagnosis of MPN [3,4], and CHIP becomes detectable at 5-15 years before MPN [5]. The initial event is the acquisition of *JAK2*V617F in a single hematopoietic stem cell (HSC) **(Fig. 1)**. The mutant HSC may persist in small numbers in the bone marrow and has to show restricted expansion in order to become detectable as CHIP; the mutant clone must expand further to actively contribute to hematopoiesis in MPN. Factors responsible for the transition from CHIP to MPN may include genetic predisposition, metabolic reprograming, additional somatic mutations, and inflammation and immunity.

Using a mouse model of MPN [6], it was shown that IL-1β is promoting efficient disease initiation by *JAK2*V617F and the progression to myelofibrosis (MF) [7,8]. Treatment with anti-IL-1β antibodies reduced MPN initiation and also the progression to MF [7,8].

Treatment with pegylated interferon(IFN)-β reduced disease in *JAK2*V617F-mutated mice [9]. IFN-β may act by exhausting mutant HSCs through acceleration of cell cycle entry and subsequent DNA damage. Loss of Dnmt3a (the most frequently affected gene in CHIP) protects V617F-positive HSCs from exhaustion and increases their self-renewal, thereby conferring resistance to IFN-β treatment in MPN mice and patient HSCs [10]. Resistance can be partially overcome by treating *JAK2*V617F/Dnmt3a-/- mice with a combination of IFN-β and azacytidine. This combination leads to eradication of *JAK2*V617F single-mutant long term-HSCs and thus is a promising approach for treatment of MPN patients who carry only the *JAK2*V617F mutation.

Cardiovascular disease, CHIP, and inflammation

(Prof. Christoph J. Binder, Medical University Vienna, Austria)

Inflammation is a major contributor to cardiovascular risk [12]. Since CHIP is associated with increased inflammatory responses, it is a risk factor for different cardiovascular diseases (CVD) and manifestations, including atherosclerosis, thrombosis, myocardial infarction, and heart failure [13]. Experimental data from mouse models demonstrate robust effects of major CHIP-associated mutations on atherosclerosis and myocardial function.

Mechanisms most prominently involve IL-1β and NETosis. In mouse models, atherosclerosis is accelerated by hematopoietic TET2 deficiency via enhanced IL-1β production [14], and by *JAK2*V617F mutation via increased IL-1β signaling and impaired efferocytosis [15,16]. Also, patients with TET2-mutant CHIP showed significant cardiovascular event reduction in response to IL-1β neutralization by canakinumab [17]. Furthermore, genetic deficiency of signaling by IL-6 (which is downstream of IL-1β) attenuates cardiovascular risk in individuals with CHIP [18]. In summary, data from mice and from interventional and genetic studies in patients establish the role of inflammation linking CHIP with CVD [19].

Oxidation-specific epitopes (OSE) present on oxidized LDL, dying cells, and microvesicles are major mediators of inflammation in CVD, upstream of IL-1β and NETosis [20]. Natural IgM antibodies with specificity for OSE are inversely associated with CVD risk and have various protective functions in CVD [21]. Boosting such antibodies could potentially be a pharmacological intervention to reduce the negative effects of CHIP, as an alternative to targeting the involved cytokines (especially IL-1β) which is associated with an increased infection risk. ■

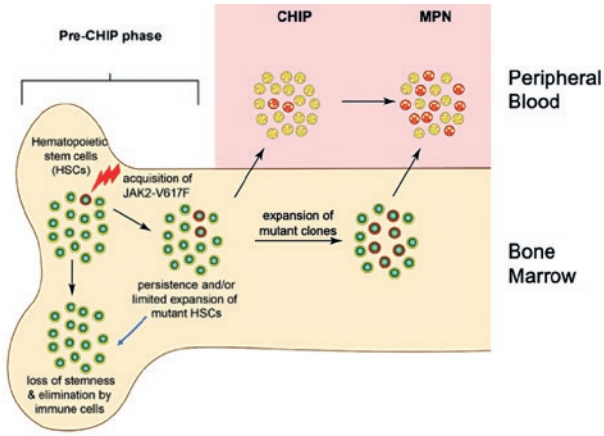

Figure 1: Clonal evolution of myeloproliferative neoplasm (adapted from ref.11)

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Treatment options in Essential Thrombocythemia (ET) and Polycythemia vera (PV)

What is available in 2023?

(Prof. Heinz Gisslinger, Medical University Vienna, Austria)

Treatment goals in ET and PV include reduction of risk of thrombosis and bleeding, avoidance of symptoms, and targeting of disease progression. Complete hematological remission (CHR) remains a challenging target with available therapy, however a retrospective study was unable to show statistically significant evidence that this was associated with reduced risk of cardiovascular events [1].

In ET, cytoreductive therapy with hydroxyurea (HU) is the standard in high-risk patients, lowering the incidence of thromboembolic events (mostly those with intermediate severity) [2]. The downside of HU therapy is an increased incidence of leukemic transformations and second cancers [3].

Anagrelide (ANA) is not inferior to HU, provided an exact diagnosis of WHO-ET vs. prefibrotic primary myelofibrosis (prePMF) has been made [4]. Also, in low-risk ET, ANA might be of advantage by efficiently lowering platelet counts [5]. However, ANA seems unable to stop progression of bone marrow fibrosis [6]. In young patients treated with ANA, highest CHR without disease progression was seen in *JAK2*-mutated ET [7].

Based on available study data, IFN-α might be a choice in ET [8]. An ongoing phase III study of ropeginterferon alfa-2b (RopegIFN) vs. ANA should clarify its position in ET therapy [9]. Guidelines recommend using HU, ANA, or IFN-α in high-risk ET on an individualized basis [10,11]. However, ANA might be preferred (probably side-by-side with IFN-α in the future).

In PV, RopegIFN showed superiority over HU regarding CHR and *JAK2*V617F allele burden in the PROUD-PV/CONTINUATION-PV studies [12]. The proportion of time spent in CHR was doubled compared to the standard treatment and requirement for phlebotomy was reduced. Together this translates into prolonged event-free survival **(Fig. 2)** and indicates a disease-modifying effect of RopegIFN [13]. In the DALIAH trial, different outcomes were reported with IFN-α, but results may be confounded by a high drop-out rate in this study [14].

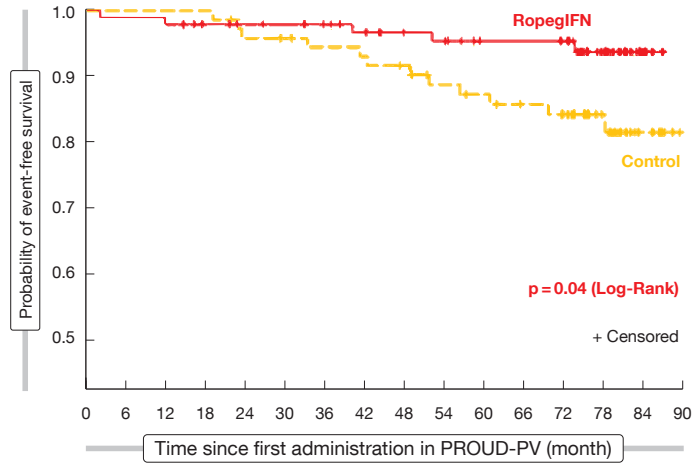

Figure 2: Event-free survival of patients in PROUD-PV/CONTINUATION-PV [13]
Risk events: death, disease progression and thromboembolic events

Ruxolitinib (RUX) treatment for PV patients with resistance/intolerance to HU may reduce the incidence of arterial thrombosis [15]. Experience tells that combining RUX with IFN may reduce time to CHR, improve molecular response and overcome IFN resistance; prospective studies are necessary to establish this combination therapy in PV.

Future prospects in PV and ET

(Prof. Rajko Kušec, University of Zagreb, Croatia)

Regarding diagnostics and prognostics of MPN, one may expect in the (near) future novel biomarkers, definition of new risk and prognosis indicators (e.g., for therapeutic efficacy, fibrosis, transformation to leukemia), and further refinement in recognition of subentities. Artificial intelligence (AI) and machine learning (ML) will be increasingly employed for diagnosing, prognosing, and explaining the complex genomics of MPN.

Automated analysis of fibrosis has already been shown to improve the assessment and classification of MPN patients [16], and ML algorithms in PV can be used for the prediction of HU-therapy failure/resistance [17] and progression to myelofibrosis (MF) [18]. However, the use of AI and ML should not be relied exclusively upon, but should be considered as a tool to assist physicians in making the diagnosis.

Regarding novel therapies, several emerging drugs are in clinical phases for PV. Examples:

- The hepcidin agonist rusfertide inhibits ferroportin and thereby decreases PV erythropoiesis through iron deprivation. In a phase II study, rusfertide was evaluated as an add-on to phlebotomy; it showed sustained control of hematocrit below 45% and eliminated requirement for phlebotomy in 84% of patients while being well tolerated [19]. A phase III trial is currently recruiting.
- Inhibition of TMPRSS6 (matriptase-2) enhances hepcidin mRNA expression. The TMPRSS6 inhibitor sapablursen (an anti-sense oligonucleotide for s.c. injection) increased hepcidin serum levels in a phase I trial [20] and is now entering a first efficacy study (NCT05143957) in PV patients.

For the future, one may expect treatment combinations of hepcidin agonists or enhancers with established cytoreductive treatments (e.g., RopegIFN).

Expression of the demethylase LSD1 is increased in cancers, including ET. LSD1 inhibits p53 methylation which abrogates cellular apoptosis. The oral LSD1 inhibitor bomedemstat restores the tumor-suppressive effects of p53. Bomedemstat is evaluated in an ongoing Phase II study in ET patients that failed to respond in at least one previous line of therapy [21]. The trial already reached its primary endpoint of platelet count reduction and showed improvement of symptoms while being generally well tolerated. Thus, bomedemstat shows promise as second-line therapy in ET. ■

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Treatment challenges in Polycythemia vera

Low-risk vs. high-risk PV

(Prof. Tiziano Barbui, FROM Research Foundation, Papa Giovanni XXIII Hospital, Bergamo, Italy)

password: IHEM23

Guidelines recommend phlebotomy and aspirin (ASA) as first-line treatment in low-risk PV patients. However, phlebotomy can actually maintain the hematocrit (HCT) values on target in only 20-30% of these patients [1]. Phlebotomy can have negative effects on quality of life, and with phlebotomy alone, thrombosis rate remains elevated [2]. Also, there is evidence that vascular complications in PV and progression to myelofibrosis can be reduced with cytoreductive drugs.

In a randomized phase II trial, low-risk PV patients were treated for 12 months with phlebotomy/ASA either alone or with additional RopegIFN at a low dose (100µg q2w) [3]. RopegIFN was safe, well tolerated, and more efficacious in comparison to a strict therapeutic phlebotomy-only policy in steadily keeping HCT on target. This advantage was maintained in a 24-month extension phase **(Fig. 3)** [4]. Also, the drug had a significant effect on surrogate markers of thrombosis and on quality of life, and reduced *JAK2*V617F allele burden. In conclusion, this study suggests significant advantages of RopegIFN over conventional treatment to control the natural history of PV in low-risk patients.

Recently, the long-term outcomes of the PROUD-PV/CONTINUATION-PV studies on RopegIFN vs. HU have been reported [5], demonstrating the benefit and safety of RopegIFN therapy in both high-risk and low-risk patients. Low-risk patients had higher hematologic and molecular response rates and were more likely to remain on long-term treatment.

These data provide further evidence for an early treatment start as recently outlined by the updated ELN guidelines [6]. Overall, available data are in favor to prescribe RopegIFN for all PV patients regardless of risk.

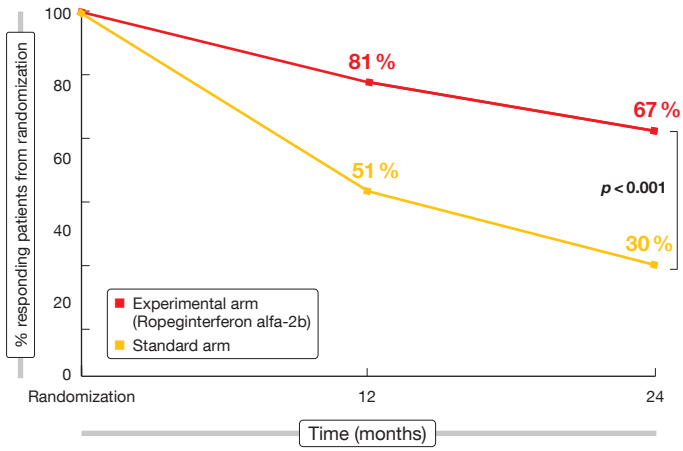

Figure 3: Event-free survival of patients in PROUD-PV/CONTINUATION-PV [13]

Splanchnic vein thrombosis (SVT) and MPN

(Prof. Jean-Jacques Kiladjian, Université Paris Cité, France)

MPN are the most common etiologies of primary SVT. In a cohort of SVT patients, 62% had an MPN as indicated by presence of the JAK2V617F mutation [7]. Importantly, many of these patients also carry prothrombotic risk factors in addition to MPN.

PATIENT CASES: HIGH- AND LOW-RISK PV

Priv.Doz. Veronika Buxhofer-Ausch, Ordensklinikum Linz, Austria

High-risk PV, case 1 – Polyglobulia and splenomegaly had been known in a male patient for some time without further investigations, when in 1/2020 at the age of 44 he presented at our hospital with portal vein thrombosis and was diagnosed with PV. Therapy with oral anticoagulation, phlebotomy, and IFN-α was initiated. Over a year later (6/2021), his PV was well controlled, but hemorrhagic complications during TIPS (transjugular intrahepatic portosystemic shunt) implantation led to acute liver transplantation. Therapy had to be changed from IFN-α to ruxolitinib; he is now (4/2023) in good condition.

High-risk PV, case 2 – Thrombo- and leukocytosis had been known in a male patient for 20 years and in the absence of cardiovascular risk factors he had experienced two myocardial infarctions at age 31; yet no further hematological investigations had been performed. At age 48 he first presented at our hospital where he was diagnosed with PV and treated with phlebotomy and IFN-α. He is in good condition now, but will need to undergo prophylactic ICD (implantable cardioverter defibrillator) implantation due to a large left ventricular aneurysm.
These cases show that MPN in young patients without CV risk factors can cause severe thromboembolic complications; thus, thorough evaluation of blood count abnormalities is essential. Early cytoreductive treatment might have the potential to avoid severe complications in otherwise low-risk patients.

Low-risk PV, case 1 – A female patient with pronounced thrombocytosis and frequent headache but no thromboembolic events received the diagnosis of PV in 4/2014 at the age of 48. She declined cytoreductive therapy and was put on phlebotomy/ASA. Over the following ~5 years under this therapy, platelet counts slowly increased, the headache got worse, and she suffered from iron deficiency and acquired von Willebrand syndrome (AvWS). She then agreed to switch to RopegIFN in 3/2020. After some initial side effects (worsening of pruritus) this therapy led to very fast improvement (reduction of platelets and leukocytes within 1-4 months, HCT on target, no phlebotomy needed, normalized iron, resolution of migraine and AvWS, good molecular response) and overall to better quality of life (QoL).

Low-risk PV, case 2 – A male patient presented with suspicious blood counts in 12/2020 at the age of 50 and was diagnosed with PV. In the absence of thromboembolic events, he was rated low-risk, but specifically asked for cytoreductive therapy on top of phlebotomy/ASA. He received RopegIFN to which he nicely responded (normalization of white blood cells and platelets, free of phlebotomy after 11 months, resolution of AvWS, decline of JAK2V617F allele burden). Side-effects like initial flu-like symptoms, joint pain, and increased pruritus were manageable and resolved over time. Very recently (4/2023) patchy alopecia areata occurred which seems controllable with a topical corticosteroid. Today he is overall in a good condition with good QoL.

Low-risk PV, case 3 – A female patient presented at the age of 50 with chest pain at the cardiology department, but coronary angiography was normal. Because of thrombocytosis and leukocytosis further hematological investigations were performed, and in the absence of thromboembolic events and polyglobulia she was diagnosed with early low-risk PV. She asked for cytoreductive therapy and was treated with RopegIFN in addition to phlebotomy/ASA. Platelets and leukocytes rapidly normalized within 2-3 months, and microcirculatory symptoms (migraine) resolved; initial side-effects were transient. She is now in a good condition and also shows good molecular response.

PATIENT CASE: SVT AND MPN

Prof. Alberto Alvarez Larrán, Hospital Clínic, Barcelona, Spain

At the age of 36, a female patient without previous diseases suffered from symptoms of intestinal ischemia due to extensive splanchnic thrombosis. Resection of part of the thin bowel due to necrosis secondary to SVT was performed and life-long anticoagulation was started.

A mutation in the prothrombin gene was found which might explain the SVT in this case. The PCR assay for the *JAK2*V617F mutation was negative. However, unprovoked SVT in a young patient without previous liver disease indicates a high probability of *JAK2*-mutated MPN, together with platelet counts in the upper limit of normality, splenomegaly, and low erythropoietin level, as seen in this patient.

About 6 years later, hematological reassessment showed normal blood counts; HCT and red cell mass were increased, but not beyond the threshold for PV diagnosis. The bone marrow showed normal cellularity apart from increased megakaryocytes. Using more sensitive qPCR, *JAK2*V617F was now detected with 10% allele burden; by NGS, no other mutations were found. Taken together, the diagnosis was *JAK2*V617F-mutated MPN of intermediate phenotype between ET and PV which is not uncommon in patients with SVT. After starting therapy with HU, the patient was put on low-dose INF-α which controlled blood values well.

To summarize, PV and ET presenting with SVT mostly correspond to *JAK2*-mutated MPN with low allele burden; normal blood counts are common, making the diagnosis difficult. Highly sensitive assays for *JAK2*V617F or NGS are recommended.

An algorithm for the diagnosis of MPN in SVT patients has been recently proposed [8]. Screening for the *JAK2*V617F mutation (present in 80% of MPN with SVT) should be the starting point of the diagnostic workup; CALR mutations are found in only ~4% of cases [9,10]. Bone marrow biopsy should be done, but is not always possible because of anticoagulation.

Search for an additional mutation using targeted next-generation sequencing (NGS) should be proposed to all patients with (suspected) MPN and SVT [11,12]. Finding such mutations can help not only with diagnosis, but also prognosis: similar to a high *JAK2* allele burden, presence of other mutations indicates a high risk of evolution to secondary MF, acute leukemia, or death [13]. In such high-risk patients, a disease modifying therapy should be considered.

Recommendations for the treatment of MPN in the context of SVT have been published recently [8]. While HU treatment failed to prevent recurrence of SVT in MPN patients in a retrospective study [13]. IFN-α and ruxolitinib have shown efficacy in small phase II studies [14,15].

Pregnancy and PV

(Prof. Martin Griesshammer, University of Bochum, Germany)

Pregnancy in PV is an increasingly frequent problem, because today women are diagnosed earlier and often delay pregnancy to later in life [16,17]. It has been recommended that all pregnant PV patients should be given low-dose ASA, and high-risk patients IFN-α; low-molecular-weight heparin (LMWH) should be given according to thrombotic risk, and in all cases also 6 weeks after delivery [18].

Using this PV-specific therapy, a dramatic increase of the live birth rate (69% vs. 6% without therapy) was reported in a small study [19]. Significantly more complicated postpartum PV courses were observed after miscarriages.

Recently, outcomes of 129 pregnancies in PV patients were analyzed; in this cohort, rates of pre-term delivery and of spontaneous abortion were doubled and the rate of stillbirths was 16-fold higher as compared to non-MPN pregnancies [20]. The analysis confirmed the significantly improved live birth rate by antenatal PV-specific therapy, particularly ASA in combination with LMWH or IFN, also in line with a previous meta-analysis [21]. Importantly, introduction of this therapy did not increase the risk of serious maternal or fetal complications.

Lifelong management of PV

(Prof. Richard T. Silver; Weill Cornell Medicine, New York, USA)

WHO diagnostic blood criteria for PV include HCT and hemoglobin (Hgb) [22]. Notably, "early PV" may be confused with ET based on HCT and Hgb alone, since isotope methods to measure red cell mass are no longer available in many countries. Therefore, bone marrow biopsy is a must to safely diagnose PV [23]. At diagnosis, spleen enlargement is uncommon, and when the spleen is palpable, it is rarely symptomatic [24]; in contrast, constitutional symptoms are usually present.

While phlebotomy is the initial treatment of PV, it causes iron deficiency and preferentially, it should not be used for maintenance therapy. Prolonged event-free survival is achieved by additional cytoreductive therapy as compared to phlebotomy alone (~20 vs. 13 years) [25].

Evidence is accumulating that recombinant IFN-α should be the treatment of choice for PV, giving rise to long-term clinical remissions. rIFN-α should be used for cytoreduction in both low- and high-risk patients to control symptoms and to prevent myelofibrosis (MF), a long-term consequence of PV. Hydroxyurea (HU), the current mainstay in PV therapy worldwide, is satisfactory, but is not disease-modifying and secondary malignancies or leukemia/MDS may arise.

A retrospective study identified MF as a major contributor to mortality in PV and showed that rIFN-α improved MF-free and overall survival in both low- and high-risk patients [25] (see **Fig. 4** for OS in high-risk PV). IFN in PV is disease-modifying [26,27]; since this is a slow process, patients should be kept on rIFN therapy for years without dose interruptions. Normal life expectancy is possible for PV patients with current care [28]; especially for patients treated with rIFN-α early. Side effects of rINF-α are acceptable when properly used and are mainly dose dependent, with drop-out rates of 15-25% in reported studies.

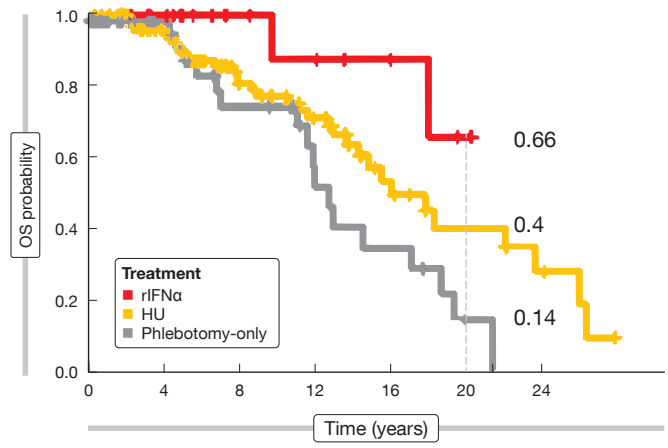

Figure 4: IFN is associated with improved OS in high-risk PV [25]

rIFN-α may be discontinued after treatment success. At Cornell, discontinuation requires *JAK2*V617F allele frequency <5% and bone marrow biopsy with "normal" cellularity and no fibrosis [29]. IFN most likely is not curative, since other mutations persist despite "eradication" of *JAK2*V617F.

Secondary malignancies

(Prof. Francesca Palandri, IRCCS St. Orsola-Malpighi University Hospital, Bologna, Italy)

password: IHEM23

In PV patients, secondary cancers are a significant cause of death which has not decreased over the last 50 years. Patients with MPNs are at an increased risk of second primary malignancies (SPM),

PATIENT CASE: LOW-RISK PV

Prof. Maria Theresa Krauth, Medical University Vienna, Austria

During regular check-up, a 38-year old male patient presented with elevated red blood cell, platelet, and leukocyte counts. He was asymptomatic but had intermittent pruritus and featured red skin patches and palpable spleen. Examination of coagulation parameters revealed acquired von Willebrand syndrome. Otherwise, no present or past comorbidities existed.

Molecular analysis revealed *JAK2*V617F positivity with an allelic frequency of ~80%; the bone marrow was hypercellular with pleomorphic megakaryocytes, but no dysplasia, blasts, or fibrosis. On these grounds, the patient was diagnosed with PV, which according to conventional stratification was regarded as low risk.

Low-dose ASA and phlebotomy was initiated to keep the hematocrit below 45%. But this therapy did not seem sufficient, since the patient required 1-2 phlebotomies per month, yet platelets and leukocytes increased. Pruritus worsened and minor bleedings occurred, so ASA was stopped.

After ~6 months, cytoreductive treatment was considered to lower phlebotomy frequency and improve the hemostatic situation, and therapy with RopegIFN (125µg q2w) was started. This led to impressive lowering of platelet and leukocyte counts and sustained HCT control. Freedom of phlebotomies was reached after 1.2 years of treatment. Pruritus completely disappeared after 4 months; spleen size returned to normal. ASA could be restarted and the dosing frequency of RopegIFN was reduced to q4w after ~1.5 years.

Today, ~2.5 years after initiating RopegIFN, JAK2V617F allelic burden went down to ~0.2%, indicating the disease-modifying capability of this therapy.

PATIENT CASE: SECONDARY MALIGNANCY AFTER TREATMENT WITH HYDROXYUREA (HU)

Prof. Alicia Rovó, Inselspital Bern, Switzerland

A male patient, aged 59, was referred to our hospital due to acute coronary artery disease and underwent angioplasty and coronary stenting. He presented polyglobulia with elevated hemoglobin and hematocrit, and slightly increased platelets. Hematological investigations led to the diagnosis of *JAK2*-positive myeloproliferative neoplasia (MPN) subclassified as PV.

The patient was initially treated with phlebotomy and low-dose ASA, but because of his cardiac ischemia also cytoreduction was indicated and HU was initiated. During follow-up under treatment with HU a good control of blood values was seen. The dose of HU was 6-7g/week, which was well tolerated; as side effect, mild skin changes (xerosis, sometimes with desquamation) occurred which were diagnosed as keratosis and managed with local treatment.

About 7 years later, the patient presented with stable MPN disease, but had papular erythematous lesions on sun-exposed areas of the face. He was then diagnosed with squamous cell carcinoma and actinic keratosis.

This finding in a patient treated with HU is actually common in daily practice, particularly in elderly patients with other risk factors for skin cancer, which is in line with the association of HU with NMSC documented by multiple case reports and clinical studies. NMSC can therefore more likely occur upon long-term HU therapy, mostly in elderly Caucasian patients.

For our patient, therapy was changed to RopegIFN. Today, 7 months later, the patient remains with good control of the MPN disease without side effects of the new therapy. Currently no new skin signs or symptoms occurred.

This case underlines, that clinicians and patients must be well aware of this potential complication. Patients who are treated with HU should undertake regular dermatological examination, particularly if they have risk factors.

particularly non-melanoma skin cancer (NMSC) [30]; skin examination is recommended, particularly if other risk factors are present. MPN patients have also an increased risk of lymphoproliferative neoplasms [31]; correct initial diagnosis and watchful follow-up is required. The occurrence of secondary MF in PV and ET patients is associated with that of SPM and NMSC [32]. Furthermore, arterial thrombosis is associated with increased risk of subsequent SPM and should trigger oncological monitoring [33].

NMSC are significantly associated with HU usage, particularly if prolonged [34,35]. Notably, study data show that pre-neoplastic lesions transform to skin cancer in all patients who continue HU [35]. Patient should be advised to minimize skin cancer risk and to report new skin lesions early; annual dermatological review should be scheduled. Regarding association between HU use and acute leukemia, there is no clear evidence but rather controversial data; it seems reasonable to adopt a conservative approach and to consider alternative treatments in particular in young patients. By contrast, no significant association was noted between HU use and lymphoproliferative disorders or solid cancers.

Use of ruxolitinib is also associated with an increased risk of skin cancers [36-38], and an association between ruxolitinib and higher risk of lymphoproliferative neoplasms has been reported [39]. Therefore, benefit to risk assessment of this therapy, adequate cancer monitoring, and consideration of therapeutic alternatives are important. Mechanisms underlying increased SPM risk during ruxolitinib mainly involve JAK1 inhibition [40].

Among cytoreductive agents, interferons have the best safety profile regarding the occurrence of second cancers. In randomized studies, no cases of SPM including NMSC have been observed so far [41-43]. In patients with previous NMSC, interferons may represent the best therapeutic option.

Overcoming treatment resistance in PV

(Prof. Florian H. Heidel, University Medicine Greifswald, Germany)

Indicators of resistance and intolerance to phlebotomy and to hydroxyurea (HU) have been clearly defined in guidelines of the European LeukemiaNet [44,45]. In contrast, criteria for resistance to *JAK2* inhibitors and IFN-α and for switching from these agents to another therapy are less clear.

A significant proportion of patients develop resistance to HU and thus carry an increased risk of disease progression and death; they need to switch to alternative treatment options in a timely manner. A study analyzed real-world evidence to identify baseline variables predictive of resistance to HU within 6-9 months after starting therapy [46]. Two standard laboratory parameters – red cell distribution width (RDW) and Hgb – were found to have predictive value for the identification of HU resistance; patients with baseline RDW ≥17% and Hgb<15.5 g/dL were most likely to become resistant to HU.

PATIENT CASE: OVERCOMING TREATMENT RESISTANCE IN PV

Prof. Michael Doubek, University Hospital, Brno, Czech Republic

A 56-year old female was diagnosed with *JAK2*V617F-positive PV in 2011. She had elevated white and red blood cells, high Hct and Hgb, and high platelet count. Splenomegaly was only detectable by ultrasound. There was no thrombosis and no comorbidities. Taken together, this was a case of low-risk PV.

Therapy was started with ASA plus phlebotomy. Due to high frequency of required phlebotomies, HU (0.5g/day) had to be added.

In 2019 progression of the disease occurred with circulating blasts at 2%, increased platelets, and palpable spleen. So, the dose of HU was raised to 1.5g/day which temporarily stabilized the disease.

Due to the high dose of HU needed to suppress myeloproliferation, it was decided in 11/2020 to add RopegIFN to the therapy. This led to a significant improvement of blood counts. HU could be discontinued after two months. Today, the patient is still under RopegIFN with normal blood counts and well controlled Hgb and HCT, decreased splenomegaly, and no toxicities; so, this therapy is being continued. Molecular response during the first year of treatment was not pronounced in this patient, but this may not matter in view of the good hematological response.

To conclude, this case illustrates the effectivity of RopegINF in patients with resistance to HU.

These predictive parameters will be validated in a prospective interventional study planned in Germany.

To overcome resistance to phlebotomy, established options include pharmacological therapy with HU or RopegIFN. In addition, the hepcidin mimetic rusfertide is an investigational drug that can reduce the requirement for phlebotomy, control HCT and red blood cell counts, and normalize iron stores (as already mentioned by Prof. Kušec).

In case of resistance to HU, available next-line therapies include ruxolitinib (RUX) [47] and RopegIFN [48]. The efficacy of RUX after IFN failure/intolerance and vice versa has not been formally tested in dedicated clinical trials, but is supported by some study data [49,50] and by real-life experience. ■

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Evolution in MPN care – the patient perspective

What has changed in MPN care?

(Prof. Haifa Kathrin Al-Ali, University Hospital Halle, Germany)

Thanks to well established guidelines and the WHO classifications [1] it is quite easy today to establish a correct diagnosis in the majority of MPN patients. Sometimes diagnosis can still be difficult, e.g., in triple-negative prefibrotic cases, or in patients with unclassified MPN pathology. There are cases were the initial diagnosis had to be corrected following additional tests (e.g., for tryptase), classical cytogenetic analysis, or reevaluation of histology [2]. In daily practice, a multidisciplinary discussion between clinicians, hemato-, and molecular pathologists is the most powerful key to establish a valid diagnosis. It was shown that the accuracy of pathology assessment can be markedly increased when clinical data are taken into consideration [3].

Today, a lot of established prognostic factors are available which in general allow an accurate prognostication in all patients. However, the current risk score for PV (which is based on age and prior thrombotic events only) is still rather basic, so there is room for improvement by incorporating other factors. In MF, clinical scoring systems like IPSS and DIPSS are available allowing for reasonable prognosis, but advanced scores like MIPSS70 include mutation data in addition [4].

Treatment goals in MPN must be patient centered. Primarily they should focus on control of symptoms and quality of life, reduction of thrombotic risk, and delay/prevention of transformation to improve survival. An individualized treatment taking patient factors but also molecular and disease-related characteristics into consideration will better meet patient needs and expectations.

Patient-relevant endpoints in clinical trials are essential and are now accepted by regulatory authorities. For example, approval of momelotinib is expected to be based on total symptom improvement as primary endpoint [5].

Finally, patient involvement in research is essential. The academic community must take a proactive stance in understanding and applying patient perspectives to improve trial design.

MPN management: Factoring in symptoms and quality of life (QoL)

(Prof. Ruben Mesa, Atrium Health & Wake Forest University, USA)

Individuals with MPN suffer from a range of difficulties: Vascular events, cytopenia, risk of progression, splenomegaly, and symptoms. All of these are important when thinking about the best treatment of MPN patients.

MPN symptoms are caused by factors coming from the disease, such as inflam-

mation and splenomegaly. In fact, fatigue and abdominal, constitutional, and microvascular symptoms are all linked to a range of biological pathways that are associated with proinflammatory cytokines. In addition, symptoms can be exacerbated by mood disorders (anxiety, depression) if these remain untreated [6].

MPN symptom assessment tools have been developed, and it was found that symptoms are prevalent and can be severe [7]. Such tools can be easily used in the clinic and allow tracking of symptoms over time [8].

The MPN Landmark Study revealed that a high proportion of MF, PV, and even ET patients felt that symptoms affected their QoL [9]. In all three conditions, fatigue was most common. In PV, pruritus and insomnia were major issues, in ET bruising, and in MF abdominal discomfort. Among most severe symptoms, also problems with sexual desire were named by MPN patients, possibly a reflection of not feeling well. There is an effect of MPN symptoms on employment: some patients reduce working hours, and some leave their job.

Symptoms are always an important piece when making treatment decisions. For example, a PV patient who is intolerant to phlebotomy and highly symptomatic (while not high-risk for thrombosis) should be considered to be treated with cytoreduction using RopegIFN.

In MF, JAK inhibitors have been approved in part due to their effect on symptoms. In low-risk MF, it depends on the situation whether to start therapy or not. If symptoms are in the foreground, ruxolitinib may be first choice; if progression is the major concern, IFN may be chosen.

In advanced systemic mastocytosis (SM), approval of avapritinib has been based on the rapid and durable improvement of the severe symptoms of this disease and its effects on QoL [10]. Also in indolent SM, the drug significantly improved symptom burden, in line with improved objective measures of disease burden [11].

In summary, MPN patients have variable but frequently challenging symptoms; these are quantifiable in reproducible manner and are linked to biology of disease. Improvement in symptoms is an important endpoint in therapeutic efficacy.

To incorporate MPN symptoms into treatment planning, one needs to consider symptoms and to measure and track them whenever initiating therapy, assessing adequacy of dose, or consider therapeutic change. One always needs to remember the potential of drug toxicity, mood disorders, or an unrelated new medical problem as source for symptoms. ■

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Selected topics in myleoid malignancies

Hot topic: Mutant CALR as a unique drug target in MPN

(Dr. Robert Kralovics, Medical University Vienna, Austria)

Somatic mutations in the gene of calreticulin (CALR) activate JAK/STAT signaling via binding of the mutated protein to the thrombopoietin receptor (MPL). These mutations are causative in about one third of patients with ET and MF. Among driver mutations of MF, CALR mutation yields the best overall survival; thus, there is a relatively large window for therapeutic intervention.

CALR frameshift mutations are confined to exon 9, yielding a neoantigenic sequence at the C-terminus. Part of the mutated protein ($CALR^{mu}$) is not associated with MPL but is secreted; levels found in the plasma of patients correlate with allele burden [1]. Drugs selectively targeting $CALR^{mu}$ are not available today, but three therapeutic approaches are emerging.

Firstly, a model of the tetrameric MPL-$CALR^{mu}$ complex identified sites that are potentially targetable by small molecules [2]. Using in silico docking, the dye hematoxylin was found to bind to the glycan pocket of $CALR^{mu}$ and disrupt its abnormal interaction with MPL [3]. Also, the ATR-CHK1 pathway was identified as a therapeutic vulnerability of CALR-mutated hematopoietic cells [4], opening additional opportunities for intervention with small molecules.

Secondly, MHC-I dependent immunotherapies involving vaccines or immune checkpoint blockade might present an opportunity in MPN. One clinical study (NCT05444530) is ongoing while others were not successful.

Thirdly, antibodies can be raised against the unique C-terminal 22-amino acid sequence of $CALR^{mu}$; they bind to the MPL/$CALR^{mu}$ complex on the cell surface. Mice carrying a chimeric murine-human CALR oncoprotein develop an ET-like phenotype, and treatment with one of these antibodies lowered platelet and stem cell counts in mutant mice [5]. Secretion of $CALR^{mu}$ did not constitute a significant antibody sink; still it is an open question if this sink might limit efficacy in human patients. Also, it is unclear what antibody format and epitope might be most effective, and a potential off-target effect (binding of secreted $CALR^{mu}$ to healthy HSCs) needs to be addressed.

As recent unpublished data show, reformating of an antibody into a chimeric antigen receptor (CAR) and its expression on T-cells also allows for specific recognition of primary $CALR^{mu}$ stem cells ex vivo and for complete and long-lasting eradication of these cells. $CALR^{mu}$ con-

centrations present in patient plasma were found to have a limited effect on primary CAR-T cell activation.

In summary, targeting the glycan binding pocket of CALR^{mu} selectively kills CALR^{mu} cells. Anti-CALR^{mu} antibodies raised against the C-terminal sequence deliver selective HSC immunodepletion in an animal model, and anti-CALR^{mu} CAR-T cells selectively kill CALR^{mu} cells *in vitro*.

Myelofibrosis (MF)

(Prof. Francesco Passamonti, University of Milano, Italy)

For a newly diagnosed MF patient, eligibility for stem cell transplantation (SCT) has to be determined, based on physiological age, performance status, comorbidities, and MF-related life expectancy [6]. For the later, different prognostic models are available. For primary MF (PMF), the older IPSS and DIPSS scores can still be recommended while the more advanced MIPSS70 model integrates prognostically relevant clinical, cytogenetic, and mutation data [7]. Differences in staging among PMF scores can impact management; in difficult cases, use of all scores plus clinical follow-up is advisable before deciding on SCT. For post-ET and post-PV MF the MYSEC-PM score is available [8].

How to manage splenomegaly in symptomatic cytopenic MF patients? If platelet counts (PLT) are low (50-100x10^9/L), the JAK inhibitor (JAKi) ruxolitinib (RUX) improved splenomegaly when started at a low dose and then was uptitrated [9]. Also, in patients with MF and anemia, good efficacy was observed with RUX at a lower starting dose [10]. In transfusion-dependent MF patients, combination of RUX with luspatercept was beneficial in a phase II study by controlling splenomegaly while lowering the need for transfusion [11].

Fedratinib, the second JAKi licensed for MF, can be given at full dose if PLT >50x10^9/L, and achieved also good control of splenomegaly if PLT were only 50-100x10^9/L [12]. Finally, pacritinib (which is licensed in the US) showed good efficacy with respect to splenomegaly and symptoms even in MF patients with PLT <50x10^9/L [13], and was also efficacious in reducing transfusion requirement in anemic patients [14].

Can we improve efficacy in JAKi-naïve MF patients? Potentially yes, but one has to wait for results of phase 3 trials; here one should ask for a clinically meaningful higher rate of spleen volume reduction and its maintenance, and for disease modification (reduction of clones and/or bone marrow fibrosis) with impact on overall survival. Based on available data, progress may come from combination therapy, e.g., of JAKi with the BET inhibitor pelabresib [15], with the BCL-2 pathway inhibitor navitoclax [16], or with selinexor [17].

Chronic myeloid leukemia (CML) – important topics

(Prof. Philippe Rousselot, Centre Hospitalier de Versailles, France)

In the revised classification of CML, acute phase at diagnosis or during treatment has been omitted and replaced by recognizing only the chronic and blast phases [18]. This new definition is better aligned with modern treatment practice.

While CML is driven by the characteristic BCR-ABL1 fusion gene, additional chromosomal abnormalities occur in BCR-ABL1-positive cells of about one third of CML patients. It is an open question whether these abnormalities (such as 11q23 rearrangement and trisomy 8, 19, or 21) are associated with progression or decreased response to tyrosine kinase inhibitors (TKI); notably, inferior molecular response to a TKI was recently observed in the case of ASXL1 mutations [19]. Also, it is unclear whether such mutations are bystanders or part of age-related clonal hematopoiesis.

With TKI therapy, deep molecular responses leading to treatment-free remission (TFR) can be reached. Following criteria for treatment discontinuation [20], about 40 % of patients become eligible after 3 years of treatment with 2nd generation (2G) TKI. After stopping treatment, long-term TFR was attained in 40-50 % of patients in several studies (see example in **Fig. 5**). Taken together, this means that only up to 20 % may reach long-term TFR. This rate is higher than with imatinib (12 %), since deep molecular responses are achieved more frequently with 2G-TKI [20,22]; also, the rate of switching to another TKI is lower when using a 2G-TKI upfront [23]. However, currently no further improvements of long-term TFR success are in sight. Actually, treatment duration and the duration in response appear to be more important for reaching TFR than the type of TKI used [24].

New drugs under development for first-line CML therapy promise faster molecular response and probably higher efficacy in high-risk patients and higher TFR rate. However, it appears that they do not offer a survival or PFS advantage compared to imatinib [25, 26]. Thus, these new drugs may be better used as 2nd or 3rd line agents in imatinib-resistant CML. A new player is the allosteric inhibitor asciminib [27] which showed convincing study results as 3rd line therapy [28]; future trials will also assess asciminib in 1st line.

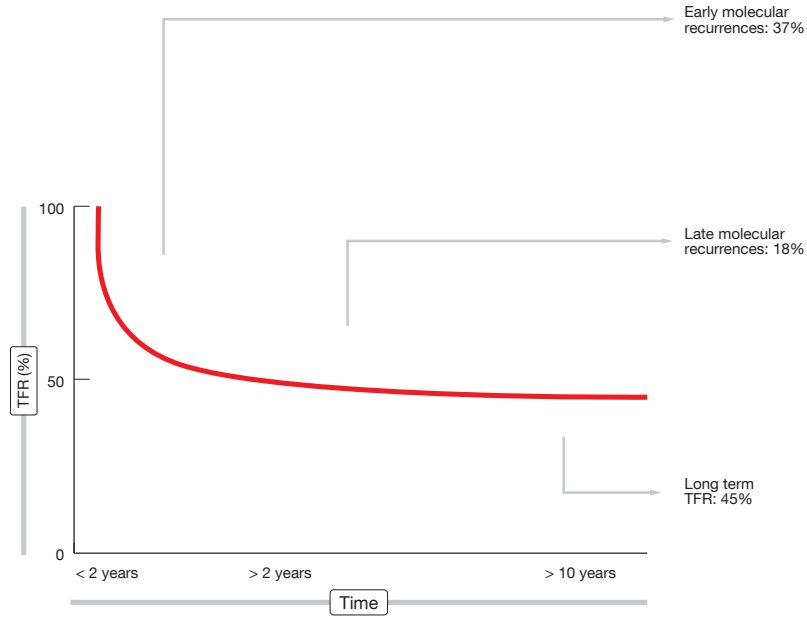

Figure 5: Molecular recurrences during TFR in CML patients [21]

Acute myeloid leukemia (AML) and MPN

(Dr. Marielle Wondergem; University Medical Center, Amsterdam, The Netherlands)

Leukemic transformation in a patient with antecedent MPN is diagnosed if there are 20 % blasts in peripheral blood or bone marrow; mostly a myeloid phenotype (AML) is observed. The 10-year risk to develop AML is high (10-20 %) in MF, while low in ET and intermediate in PV. The pathogenesis involves accumulation of additional genetic events, mostly after the JAK2V617F mutation.

Post-MPN AML is not the same as *de novo* AML. The rate of erythroblastic and megakaryoblastic morphology is higher and there are distinct chromosomal and molecular features; the survival is poor (3-6 months). Risk factors include older age, and signs of disease progression, like increasing leukocytosis and blast counts, and worsening thrombocytopenia or anemia. Some older MPN therapies (P32, busulphan) can induce AML while there are conflicting data for others, especially hydroxyurea. Chromosomal abnormalities and co-occurrence of mutations increase the risk of progression to AML.

Diagnosis is based on increasing anemia/thrombocytopenia and blasts counts and may be more difficult due to erythroid or megakaryocyte morphology and sometimes specific findings like lytic bone lesions. NGS can be used for risk assessment and to choose targeted treatment.

Prevention is the best strategy: Allogeneic SCT before progression to AML in fit patients leads to better outcome [29]; also, no induction therapy (with added toxicity) is necessary. When AML has occurred, allogeneic SCT as consolidation following induction therapy can be done but is not for all patients and has only a 10 % 5-year OS rate [30]. Induction therapy may involve intensive chemotherapy or hypomethylating agents (HMA; alone or combined with ruxolitinib). Experience with venetoclax induction in post-MPN AML is disappointing [31, 32].

Treatment remains difficult. Among targeted therapies, IDH1/2 inhibitors showed objective response rate 40 % in post-MPN AML [33], and in studies in *de novo* AML showed even better responses in combination with HMA. For TP53-mutated AML, promising immunotherapeutic approaches are underway in early clinical studies [34].

Eosinophil malignancies

(Prof. Andreas Reiter; University Hospital Mannheim, Heidelberg University, Germany)

Myeloid/lymphoid neoplasms with eosinophilia (M/LN-Eo) are clonal diseases characterized by dysregulated tyrosine kinase (TK) fusion genes. Over 80 of these fusions are currently known, however, some of them are difficult to detect (cytogenetically cryptic fusion genes); their impact on prognosis and treatment largely varies.

About half of M/LN-Eo patients carry the *FIP1L1-PDGFRA* fusion; *PDGFRB* fusions are also frequent. In these cases, complete remissions (CR) are achieved with the TK inhibitor (TKI) imatinib at a low dose (100 mg/day); in the chronic phase of disease, survival rates are high (85 % at 20 years). About 15-20 % of patients present in a myeloid/lymphoid blast phase (in the bone marrow or extramedullary) already at diagnosis; still, survival is high with imatinib (70 % at 10 years). After stopping TKI therapy, treatment-free remission over ~2 years can be expected, with CR obtained again after restart of therapy [1]. Primary and secondary resistance to imatinib is very rare.

Patients with M/LN-eo and *FGFR1* fusions have quite different characteristics: they mostly present in primary blast phase (in the bone marrow or frequently extramedullary) and have a median survival of only 10 months [2]. The phenotype of the disease varies depending on the fusion partner [3]. So far, allogeneic stem cell transplantation (SCT) was the only effective therapy but the TKI pemigatinib may offer a long-term treatment option according to phase II study data [4]. Also for M/LN-Eo with other TK fusion genes, e.g. *JAK2*, *ETV6-ABL1*, the eligibility for allogeneic SCT should be evaluated.

Chronic eosinophilic leukemia (CEL) is a rare clonal disease associated with point mutations, especially with *KIT* D816V (then diagnosis of systemic mastocytosis with associated CEL, SM-CEL), *STAT5B*-N642H and rarely also *JAK2*V617F. CEL features poor prognosis.

Non-clonal, reactive eosinophilia (e.g. hypereosinophilic syndrome, HES) is ~10-times more prevalent than clonal eosinophilia. HES is characterized by durable eosinophilia >1,5 x 10^9/l in blood and organ infiltration/dysfunction; besides an idiopathic form, there is a lymphocytic variant driven by clonal T-cells. At diagnosis, patients need to be carefully examined for (multiple) organ involvement and dysfunction (to differentiate from single organ involvement). If organ dysfunction is established, oral corticosteroid-based (OCS) immunosuppressive therapy is indicated, especially in the case of heart involvement. Alternatively, anti-IL5 antibodies, e.g. mepolizumab, present an effective therapy of HES [5]; however in severe disease, a combination with OCS-based immunsuppression may still be needed. ■

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