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Meeting Report IHEM 2022

MYELOPROLIFERATIVE NEOPLASMS: SCIENTIFIC ADVANCEMENTS AND IMPACT ON CLINICAL PRACTICE

Report from the 15th International Hematology Expert Meeting (IHEM)
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Preface

Dear Colleagues,

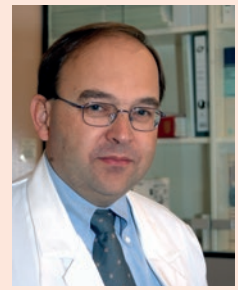
The 15th International Hematology Expert Meeting, which was conducted by CEMPO as a hybrid meeting from 5th to 7th May 2022, drew over 400 participants from 20 countries who had the opportunity to listen to many stimulating talks offering new perspectives in the management of myeloproliferative neoplasms (MPNs).

Patients affected by MPNs, especially polycythemia vera (PV) and essential thrombocythemia (ET), 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 2022 focusing on molecular mechanisms of MPNs, clinical aspects as well as patient cases.

Additional topics of potential relevance in the years to come include combination therapies and enhanced individualization pertaining to targeted therapies and improved selection of treatment by patient characteristics.

Moreover, as MPNs and cardiovascular conditions share risk factors such as smoking, very early treatment prior to the recognition of overt disease might prove to be an approach that provides ample health benefits.



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

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Molecular Pathogenesis of Myeloproliferative Neoplasms (MPN)

MPNs are characterized by the aberrant clonal proliferation of one or more hematopoietic cell lineages, predominantly in the bone marrow. While driver mutations in hematopoietic stem cells (HSC) – in particular in the *JAK2*, *CALR*, and *MPL* genes [1] – are the underlying cause of MPN, the expansion of mutant HSC is driven by additional factors, including persistent inflammation [2].

Inflammation in MPN: Spotlight on IL-10

MPN patients have high levels of inflammatory cytokines, some of which drive disease symptoms and may also promote expansion of the neoplastic clone. Prof. Angela Fleischman (University of California, Irvine) found that MPN monocytes show persistent and elevated TNF production in response to TLR agonists [3]. This is due to defects in the signaling pathway of the anti-inflammatory cytokine IL-10, resulting in insufficient suppression of TNF. Thus, a dampened response to IL-10 contributes to chronic inflammation in MPN.

Moreover, IL-10 plays a key role in HSC proliferation. Prof. Fleischman presented unpublished work showing that blockade of IL-10 receptor signaling in mice increases the selective advantage of HSCs carrying the *JAK2*-V617F mutation (a driver in many MPN) over wild-type cells. Future work will address whether defective IL-10 receptor signaling may underlie the predisposition to acquire MPN.

Gut microbiome and diet in MPN

Prof. Fleischman evaluated the role of the gut microbiome in MPN and found decreased counts of Phascolarctobacterium faecium, a microbe previously associated with reduced inflammation [4]. This may contribute to the chronic inflammation central to MPN.

Since a Mediterranean diet has proven to be beneficial in metabolic diseases, which are characterized by chronic subclinical inflammation, a pilot study in MPN patients was performed. Indeed, it appeared that this diet may be beneficial for symptom burden in MPN.

Overall, it appears that diet and manipulation of the microbiome are potential low-risk approaches to reduce inflammation in MPN.

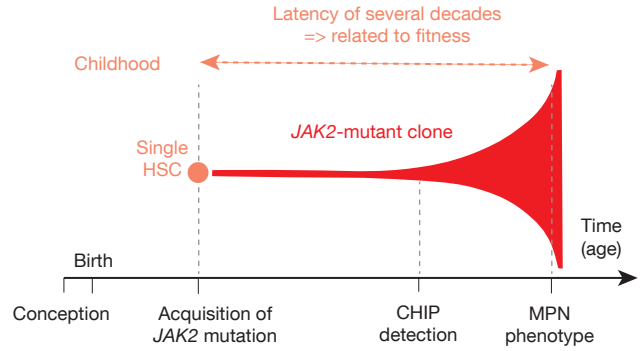

Figure: Timeline of clonal evolution in MPN [11]

Clonal evolution in MPN

MPN is a clonal disease originating from a single HSC, in which a somatic mutation in one of the three phenotypic driver genes is acquired. However, as pointed out by Prof. Radek Skoda (University Basel), the *JAK2*-V617F mutation is also frequently found in non-MPN individuals with clonal hematopoiesis of indeterminate potential (CHIP) [5-8]. This indicates that the acquisition of the driver mutations is not the limiting factor for initiation of MPN.

The *JAK2*-V617F mutation is often acquired early in life, as recent studies showed [9,10] (**Figure**). CHIP can be detected ~5–15 years before MPN onset [12], but the conversion rate from CHIP to MPN is low. The factors determining conversion include inflammation, but also genetic predisposition, acquisition of additional somatic mutations, and metabolic reprograming.

To study such factors, the group of Prof. Skoda developed a mouse model of *JAK2*-V617F-driven MPN where monoclonal disease is initiated with a single HSC using bone marrow transplantation at limiting dilution [13]. Using the model, it was shown that loss of the epigenetic regulator *EZH2* (which also occurs in patients) increases MPN disease initiation [14] – an example of a somatic mutation affecting transition to MPN. Furthermore, in unpublished work it was shown that IL-1b is required for efficient MPN initiation – an example of the impact of inflammation. Importantly, both EZH2 and IL-1b in addition promote the progression to myelofibrosis in the late expansion stage of MPN.

In MPN, additional mutations can be acquired in the same HSC clone before or after the driver mutation, or in separated clones [13]. The order of acquisition may influence the phenotype and the evolution. New single-cell technologies enable clonal architecture determination; this may provide additional information for risk stratification and prognosis.

An interesting question is whether there is a chance for early intervention that could prevent conversion to MPN. Prof. Skoda pointed out that the low frequency of conversion poses a problem here: treating all CHIP patients would mean treating many who will never actually get manifest MPN. So, the challenge will be to identify those at high risk of conversion. ■

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Essential Thrombocythemia

Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterized by enhanced megakaryopoiesis in the bone marrow and increased release of platelets into the peripheral blood. Therapeutic goals include symptom control, prevention of thrombosis and hemorrhage, and minimization of disease progression.

Unmet need in ET

In ET, preventing or delaying disease progression is crucial, especially in young patients with high molecular risk. Dr. Alberto Álvarez-Larrán (Hospital Clínic, Barcelona) pointed out that conventional therapy with cytoreduction and antiplatelet therapy fits mainly ET with heterozygous *JAK2* mutation. However, based on next-generation sequencing (NGS) analysis, only ~50 % of ET patients have *JAK2*-positive disease (**Table**) [1]. Thus, NGS provides useful information regarding prognosis and might help in therapy personalization.

Dr. Álvarez-Larrán asked for the definition of treatment algorithms and objectives of therapy for triple negative ET. For TP53 and chromatin/spliceosome mutated ET in particular, new therapies would be needed.

Patients with *CALR*-mutated ET are younger and more frequently have extreme thrombocytosis as well as a higher rate of myelofibrosis progression; the disease could be considered a distinct entity with different therapy objectives and needs. For high-risk ET patients, guidelines of the European LeukemiaNet (ELN) recommend cytoreductive therapy [2]. However, Dr. Álvarez-Larrán noted that the time to complete hematological response (CHR) is longer and the duration of CHR is shorter for *CALR*-positive disease [3]. Targeting *CALR*-mutated MPN progenitors with a neoepitope-directed monoclonal antibody might be a therapeutic strategy in the future [4].

Treatment of ET

Prof. Rajko Kušec (Dubrava University Hospital, Zagreb) pointed out that one needs to carefully distinguish ET from pre-fibrotic PMF and masked PV. Before starting treatment of newly diagnosed ET, the risk for thrombosis/hemorrhage needs to be assessed, e.g., by use of the rIPSET score [5]. For reducing the risk of thrombosis in ET, lowering platelet counts is essential [6]. The treatment goal for cytoreduction should be generally set to < 400 x109/L, while 600 may be allowed in case of intolerance to cytoreductive drugs. First-line therapy for high-risk ET patients according to ELN guidelines is hydroxyurea (HU), interferon(IFN)-α [7], or anagrelide [8].
Prof. Kušec illustrated his treatment strategy with same patient cases:

- A female *JAK2*-positive ET patient diagnosed at age 34 with rIPSET = low, with no symptoms or comorbidities is doing well for 13 years with acetylsalicylic acid (ASA).
- A female *JAK2*-positive ET patient diagnosed at age 75 with rIPSET = high and several comorbidities has been given HU now for 6 years, starting one year after diagnosis, to keep platelet counts within range.
- A male patient with *CALR*-mutated ET, aged 41 years at diagnosis, with extreme thrombocytosis was treated with anagrelide, causing a steady decline of platelet counts. Upon COVID19 infection (CVI), platelets went up again, in line with reports of increased venous thrombosis risk in ET due to the infection [9].
- In hematologically stable patients, symptoms may fluctuate, influenced by other health conditions. Prof. Kušec showed a patient whose symptoms increased due to CVI and highlighted the importance of registering symptoms in ET using a simple questionnaire [10].
- A female *JAK2*-positive patient with splanchnic vein thrombosis but normal blood counts was not given cytoreductive therapy since the benefit of cytoreduction in such patients is uncertain. Approximately half of the patients do not develop overt MPN, and the clinical course is mostly indolent [11].

Finally, Prof. Kušec stressed that it is crucial to educate patients about their disease and establish good communication, taking into account patient needs and expectations. ■

TABLE
ET – Molecular classification

Genotype	Frequency (%)
Heterozygous JAK2	45
Homozygous JAK2	< 5
CALR-pos.	20
MPL-pos	5
TP53 disruption/aneuploidy	< 2
Spliceosome/chromatin mutation	8
Other driver mutation	< 5
No known driver mutation	10

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Early Intervention in Polycythemia vera – Aiming for disease modification

Polycythemia vera (PV) is characterized by unregulated malignant proliferation of hematopoetic stem cells, leading to increased blood counts of erythrocytes and in ~50 % of cases also to leukocytosis and thrombocytosis. Myeloproliferation is driven by genetic alterations whereby mutation V617F in *JAK2*-tyrosine kinase alone is sufficient to trigger PV. With age, the frequency of additional mutations contributing to PV increases [1].

Differentiation of *JAK2*-V617F-mutated HSCs

How does *JAK2*-V617F impact native human hematopoiesis? This question was addressed by Dr. Ann Mullally (Dana Farber Cancer Institute, Boston) using single-cell profiling of HSCs from MPN patients [2]. The analysis revealed that the somatic mutation actually occurs in a single HSC, decades before diagnosis of MPN. *JAK2*-V617F increases the expansion rate of HSCs in MPN patients, meaning that the malignant cells have increased fitness in native human hematopoiesis. Moreover, in HSCs *JAK2*-V617F induces a megakaryocyte-erythroid differentiation bias leading to enhanced production of respective progenitor cells. The *JAK2*-mutant allele fraction varies substantially in different myeloid compartments within the same patient [2]. Also, peripheral blood allele fraction does not reflect HSC allele fraction.

Targeted cytoreductive therapy

Targeted depletion of *JAK2*-mutated HSCs can be achieved by therapy with IFN-α. A recent study by Dr. Mullally examined the molecular response to IFN-α in *JAK2*-mutated vs. *CALR*-mutated MPN [3]. In *JAK2*-positive patients with CHR, a significantly greater reduction of V617F allele burden occurred compared to those failing to attain complete response. By contrast, the mutated allele burden in MPN patients with *CALR* mutation was not significantly affected by IFN-α therapy, regardless of the hematological response. This demonstrates a specific molecular response to IFN-α in *JAK2*-mutated disease.

The study also investigated the occurrence of new mutations during two years of IFN-α therapy [3]. DNMT3A-mutated clones/subclones emerged on IFN-α treatment and were enriched in those patients not achieving CHR.

Guidelines for cytoreductive therapy

Until recently, cytoreductive therapy of PV was recommended only for high-risk patients, but not for those with a low risk (i.e., age < 60 and no history of thrombosis). However, the risk of thrombosis is also increased in low-risk PV as compared to the non-MPN population [4], and phlebotomy alone is not adequate to steadily keep the hematocrit (HCT) on target (< 45 %) in real-world clinical practice [5]. In addition, the presence of leukocytosis and thrombocytosis in many PV patients and the symptom burden of the disease need to be considered [6]. As reported by Prof. Tiziano Barbui (Ospedale Papa Giovanni XXIII, Bergamo), the European LeukemiaNet (ELN) therefore now recommends cytoreductive therapy also for certain subgroups of low-risk PV patients (**Box**) [7].

Choice of therapy for cytoreduction

Low-risk PV patients, which fulfill criteria for cytoreductive therapy, should be treated with IFN-α as recommended by

CYTOREDUCTIVE THERAPY IN LOW-RISK PV [7]

Recommended in case of …
- Poor tolerance to phlebotomy
- Inadequate haematocrit control with phlebotomies (need ≥ 6/year)

To be considered in case of …
- Progressive leukocytosis
- Extreme thrombocytosis
- High symptom burden
- Relevant cardiovascular risk

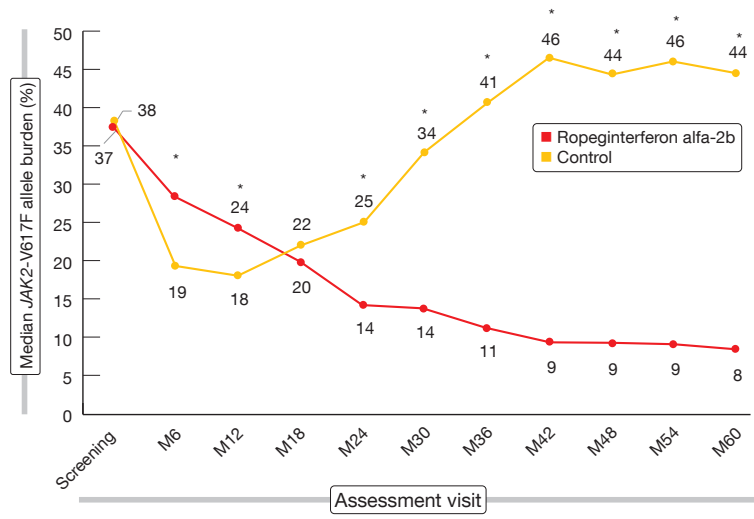

Figure: Median *JAK2*-V617F allele burden of patients in PROUD-PV/CONTINUATION-PV [10]

the updated ELN guidelines [7]. In support, Prof. Barbui showed the interim analysis of a Phase 2 study that compared therapy with Ropeginterferon (RopegIFN, BESREMI®) to phlebotomy in low-risk PV patients [8]. RopegIFN provided a significant advantage, both regarding HCT control and disease progression. Moreover, RopegIFN therapy led to normalization of white blood cell (WBC) and platelet counts, improvement of PV symptoms, and to statistically significant reduction of *JAK2*-V617F allele burden after one year.

In addition, the results from the seminal Phase 3 studies PROUD-PV and CONTINUATION-PV must be considered: here, the proportion of patients achieving long-term CHR was higher with RopegIFN than with hydroxyurea (HU) [9]. Especially impressive was the steady decline of *JAK2*-V617F allele burden under RopegIFN, with a concomitant increase in the control group (**Figure**) [10].

As reported by Prof. Barbui, for high-risk PV patients the expert panel recommends starting cytoreductive therapy with RopegIFN or HU in first-line, and ruxolitinib or RopegIFN in second line, on the basis of age, spleen size, symptoms, history of skin cancers, and patients preference.

RopegIFN therapy: Practical considerations

RopegIFN is approved as first-line monotherapy for adults with PV without symptomatic splenomegaly [11]. As Prof. Martin Griesshammer (Johannes Wesling Medical Center, Minden) pointed out, clinicians appreciate this very broad label. However, careful management of its use is required, especially when also treating more of the low-risk PV patients. Recommended dosing schemes for RopegIFN are given in the **Table**. Once stabilization of the hematological parameters is achieved, the q2w dose should be maintained for at least 1.5 years. Thereafter, the dose can be adjusted and/or the interval extended. For elderly patients, adjustment of the initial dose is not required [12].

TABLE
Recommended dosing of RopegIFN

Previous cytoreductive therapy	RopegIFN Dosing
None	Individualized escalation: Begin with 100μg q2w, stepwise increase by 50μg; max. 500μg q2w
HU	Begin with 50μg q2w, stepwise increase; in parallel, taper HU as appropriate
Other pegylated IFN-α	Multiply monthly dose of other pegylated IFN-α with 0.7

Regarding side effects of RopegIFN, Prof. Griesshammer highlighted the following aspects:

- IFN-α therapy can have hepatotoxic effects. Liver enzymes should be regularly monitored, but mild elevations should not be a concern.
- In the case of severe renal insufficiency, a reduced RopegIFN starting dose should be used; only terminal renal insufficiency is a contraindication.
- Hypo- and hyperthyroidism and thyroiditis occur relatively frequently under RopegIFN. TSH should be monitored in the first place; if it is normalized, RopegIFN can be continued.
- Contraindications to IFN-α include:
  - severe psychiatric disorders
  - (severe depression, suicidality)
  - severe pre-existing cardiovascular diseases and recent stroke or myocardial infarction – autoimmune diseases

In rare cases, severe ocular diseases under IFN-α have been observed. Upfront check with an eye specialist is advisable in case of suspected retinal disease.

In summary, Prof. Griesshammer stated that RopegIFN is effective, safe, and well tolerated. In clinical practice one needs to keep an eye on potential adverse events, e.g., affecting liver, CNS, skin, and the endocrine and immune system. Importantly, careful dosing pays out on the long run.

Prof. Griesshammer showed with a few examples how the overall situation of a PV-patient needs to be considered when making therapeutic decisions on the use of RopegIFN:

- A 22-year-old female newly diagnosed PV patient with symptomatic portal vein thrombosis, hepatopathy, and moderate splenomegaly.
  - In this case, anticoagulation was started immediately. Also, HU was given initially for stabilization, but after 3 months switched to RopegIFN.
- A 33-year-old female PV patient with recent cerebral ischemia. Heavy smoker with hypertension and M. Basedow, variable compliance.
  - With this profile, the patient is not a good candidate for RopegIFN, and HU therapy was maintained.
- A 65-year-old male PV patient, for one year on RopegIFN (200 μg q2w), develops mild depression, eosinophilia (of unclear cause), and signs of autoimmunity.
  - In this case, the dose was reduced to 50 μg q2w, then q3-4w. PV remained well controlled. ■

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Polycythemia vera (PV): Patient Cases

RopegIFN for low-risk PV – Academic question or reality

Dr. Philippe Schafhausen (University Medical Center Hamburg Eppendorf) addressed this question by presenting two patient cases:

- A male patient, diagnosed with PV at the age of 41 with no history of thrombosis (classified as 'low risk') but symptomatic (night sweats, tinnitus, headache, pruritus) was initially treated with phlebotomy and low-dose aspirin. Half a year later, HCT was still > 45 % and symptoms persisted despite phlebotomy every four weeks. Therefore, cytoreductive therapy with pegylated IFN-α was started. However, after six months, therapy had to be stopped due to side effects (depression, fatigue), and the patient was switched to HU. After > 2 years on HU, symptoms persisted despite good HCT control, and therapy was changed to ruxolitinib. Ruxolitinib controlled HCT well, but WBC and platelet counts increased, and some symptoms persisted. Finally, after almost two years, the patient was switched to RopegIFN which controlled blood cell counts well and led to rather an improvement of symptoms over the last ~2.5 years.
- Another male low-risk PV patient received cytoreductive therapy due to need for frequent phlebotomy and symptoms, starting three years after being diagnosed at the age of 37. He also went through a sequence of therapies: from pegylated IFN-α to HU to ruxolitinib and back to IFN-α. Ruxolitinib was stopped because of planned fatherhood. As a consequence,, he was switched to RopegIFN, then had a well-controlled HCT for the last two years and is now phlebotomy-free for seven months.

Dr. Schafhausen stated that also in the low-risk group of PV patients there are clearly individuals in need of cytoreductive therapy. However, the established risk factors (age or thromboembolism) alone are not sufficient for differentiated treatment decisions. In this regard, validation of additional parameters currently under discussion (leukocytosis, thrombocytosis, *JAK2* allele burden, cardiovascular risk factors etc.) is needed to help optimization of therapeutic strategy.

Suboptimal response to HU

Dr. Sotirios Papageorgiou (University of Athens) presented the case of a male PV patient who was diagnosed at age 58, and ~5 years later was treated with HU because of increased need for phlebotomies. After six months on HU, the response was deemed as suboptimal: the patient was still in need of regular phlebotomies to maintain hematological control, had increased spleen size, and developed symptoms. Therefore, HU was withdrawn and RopegIFN was started. After four months, blood counts had normalized, and no more phlebotomies were needed.

After ten months on RopegIFN, the patient complained of fatigue and constipation; TSH was elevated. Since hypothyroidism was diagnosed, RopegIFN was temporarily withheld. Once hypothyroidism had subsided on oral thyroxine, RopegIFN was restarted.

As of recently, blood counts are normal, and the patient is free of phlebotomy and PV symptoms. *JAK2*-V617F allele burden is down to 8.2 % only (from ~42 % three years ago).

The case illustrates safety and efficacy of RopegIFN, and the independence of CHR and molecular response from HU pretreatment status, in line with data from the Phase 3 studies [1].

Switch Cases in PV

Dr. Thamer Sliwa (Hanusch Hospital, Vienna) reported on patients requiring a switch to RopegIFN due to adverse events under previous therapies.

A male patient aged 67 years, with moderate splenomegaly fulfilled criteria for a PV diagnosis (elevated hemoglobin, HCT, erythrocytes, and leukocytes; lowered erythropoietin; detection of *JAK2*-V617F). Therapy was started with pegylated IFN alpha-2a. However, after 2½ years the patient experienced myalgia, so the dose was reduced. Subsequently, he developed eczema (atopic dermatitis), so IFN-treatment was stopped, and drug therapy was paused for eight months. Since the patient now required frequent phlebotomies and HCT could not be controlled with HU, RopegIFN was initiated (starting dose of 75 µg, in the first two weeks together with HU). After four months, a maintenance dose of 150µg was reached which was sufficient for HCT control without the further need for phlebotomies; the patient reported improved quality of life and no side effects. HCT levels which had increased after pausing therapy are now within the normal range again.

A male, 50-year-old patient with ankylosing spondylitis was diagnosed with PV. He had splenomegaly, symptoms of pruritus and arthralgia, and elevated blood parameters (high HCT and hemoglobin, leukocytosis). In this younger patient, NGS was performed and identified passenger panmyeloid mutations (IDH1, DNMT3A) in addition to *JAK2*-V617F. The patient was initially treated with ASA and phlebotomy, but the latter was not tolerated due to syncope. Therefore, he was switched to HU plus pegylated IFN alpha-2a and after five months changed to IFN monotherapy. While CHR was reached and symptoms were controlled, his spondylitis deteriorated a few months later, and the patient suffered from arthralgia forcing an IFN discontinuation. The patient was put on ruxolitinib which achieved HCT and symptom control. Unfortunately, the patient had two episodes of herpes zoster and also developed cystitis during the following ~2 years of ruxolitinib therapy. Therefore, the patient was finally switched to RopegIFN (with careful dose escalation, initially with concomitant HU) - he is now without rheumatological symptoms for the last year.

Combination therapy

IFN-α and the JAK1/2-inhibitor ruxolitinib may synergistically act in tumor cell killing, and also alleviate side effects of

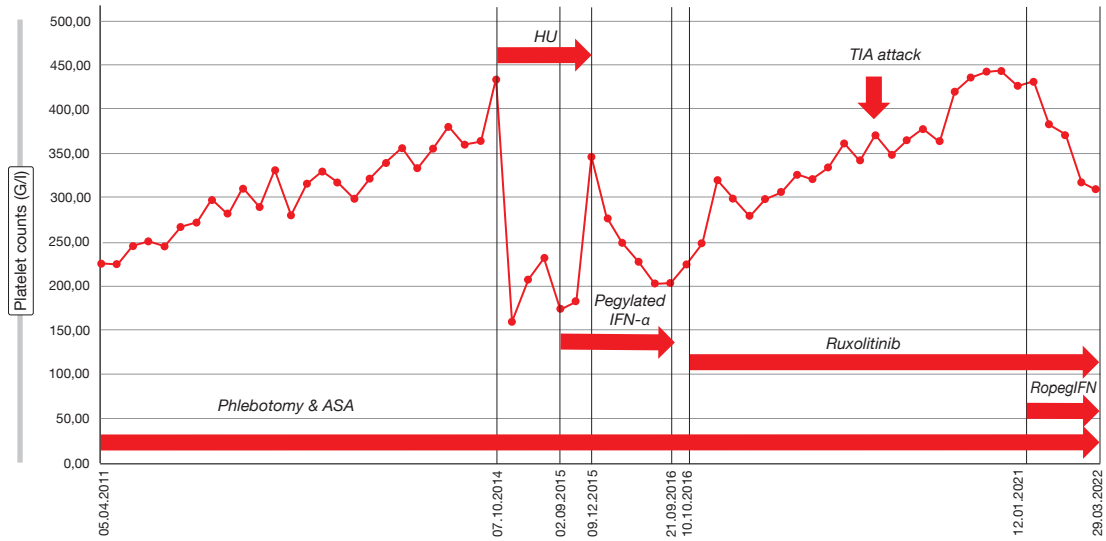

Figure: Course of platelet counts in a PV patient

the respective monotherapy [3]. Also, it has been suggested that ruxolitinib may overcome inflammatory-resistance to IFN-α [3]. Following the first case report [2], a Phase 2 study of IFN-α plus ruxolitinib combination therapy included PV and myelofibrosis patients, many of which were IFN-intolerant and/or refractory [4]. Combination treatment rapidly improved cell counts and decreased *JAK2*-V617F burden.

Prof. Heinz Gisslinger (Medical University of Vienna) presented the case of a male PV patient, at diagnosis aged 58 years and with symptoms. Under initial therapy with phlebotomy and ASA, platelet counts (**Figure**) and WBC were continuously increasing. Therefore, cytoreductive therapy was started, first with HU, then pegylated IFN-α; both controlled HCT and blood counts well but had to be discontinued due to intolerance (HU) and occurrence of panic attacks (IFN-α). Therapy was switched to ruxolitinib (5 mg bid); under this treatment, the patient had a stable HCT, but WBC moderately and platelet counts strongly increased (**Figure**); also, a transitory ischemic attack (TIA) occurred, indicating ruxolitinib resistance. Therefore, RopegIFN (100 µg q4w) was added which led to a drop of platelet (**Figure**) and leukocyte numbers; the patient was without any symptoms during this combination therapy, psychiatric symptoms did not reappear.

Prof. Gisslinger concluded that combination therapy is a reasonable second-line option in therapy-resistant PV. Ruxolitinib mitigates IFN-triggered autoimmunity and mood disorders, while IFN counteracts the immunosuppressive effect of ruxolitinib.

Efficacy of interferon in PV – A matter of dose?

Dr. Joachim Göthert (University Hospital Essen) pointed out that the IFN-α response in PV is not strictly dose-dependent. In an *in vitro* study, RopegIFN inhibited the proliferation of MPN-derived *JAK2*-mutant cell lines, but no dose-dependence was observed in the range tested [5]. *In vivo*, similar molecular and hematological responses can be achieved with quite different doses in different individuals. To illustrate this, Dr. Göthert showed two patients who achieved a comparable decline of the *JAK2*-V617F allele burden after treatment with RopegIFN at doses of 100 µg q2-3w and 500 µg q2w. This is also reflected in the data from the Phase 3 studies of RopegIFN where individualized dosages in the range of 100 to 500 µg were used to control disease [6].

It appears that response to IFN-α is mainly determined by multiple host factors. In particular, germline genetic factors have been shown to influence the outcome of IFN-α therapy, especially the IFN lambda 4 (IFNL4) diplotype status [9]. Furthermore, immunological determinants may play a role, e.g., the presence of anti-IFN antibodies in MPN patients has been shown to greatly affect molecular and hematological responses [8]. Finally, the pleiotropic action of IFN-α (promotion of HSC cycling, induction of apoptosis, suppression of megakaryopoiesis, inhibition of cell growth and angiogenesis) may explain why its action can extend over a wide dose range [9]. ■

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Chronic Myeloid Leukemia (CML) – Set the Scene

TKIs in CML – A backbone with limitations

Starting with the ground-breaking success of imatinib [1], tyrosine kinase inhibitors (TKIs) targeting the oncogenic BCR-ABL1 kinase have revolutionized CML therapy in the last 20 years. Long-term life expectancy in CML patients in the chronic phase (CML-CP) is now > 80 %. Imatinib and the second-generation TKIs nilotinib, dasatinib, and bosutinib are approved for first-line treatment of CML-CP; ponatinib (and soon asciminib) expand the spectrum in second and further treatment lines.

Dr. Frank Stegelmann (University Hospital Ulm) explained that faster and deeper responses are achieved with second-generation TKIs compared to imatinib [2-4], and that this advantage may extend over many years [5,6]. However, for the primary choice of the TKI also the individual co-morbidities of the patient, specific side-effects of the TKIs, and individual treatment goals must be taken into account.

Each TKI has a typical profile of side-effects. One needs to be aware of specific adverse events, e.g., cardiovascular events under nilotinib therapy in elderly patients [5], the occurrence of pleural effusion under dasatinib [3], or of diarrhea with bosutinib [4].

The goal to obtain treatment-free remission (TFR) deserves special attention. TFR can be attained in ~25–30 % of all newly diagnosed CML-CP patients with careful management but requires regular BCR-ABL1 monitoring. About 10–20 % more patients under nilotinib or dasatinib become eligible for treatment stop compared to Imatinib after five years of therapy [7]. Detailed guidelines for the management of TKI discontinuation are available [8].

Despite the success of TKI, 6 % of patients progress to blast phase. Outcome in advanced-phase CML is poor; if possible, patients need to proceed to allogeneic stem cell transplantation (SCT) after debulking with chemotherapy +/- TKI.

Interferon in CML – a critical review of evidence

BCR-ABL is the causative genetic aberration in CML which transforms stem cells, only.

While in CML patients there is a dramatic short-term response to BCR-ABL inhibitors, transformed stem cells remain viable in a quiescent state in their presence [9]. As explained by Prof. Andreas Burchert (Marburg University Hospital), this is why BCR-ABL1 inhibition fails to eradicate CML, with only ~20 % of all CML patients eventually able to discontinue TKI therapy after prolonged treatment. Persistence of CML under TKI therapy is enabled by low BCR-ABL1 expression levels in stem cells [10], inactivity of the kinase, and kinase-independent survival.

So how to tackle these TKI-insensitive stem cells? It has been shown that sustained remission after BCR-ABL1 inactivation depends on an immune-intact host [11]. IFN-α triggers and maintains T-cell immunity; it also induces apoptosis of cycling stem cells – so could it be useful here? Clinical data show that IFN-α is actually quite inefficacious in CML, with complete response rates of only 5–20 %. However, when stopping IFN therapy in complete responders, loss of response occurs very slowly; low levels of minimal residual disease are associated with continuing remission [12].

Prof. Burchert concluded that immunological control of CML may be gained from IFN-α therapy. Actually, CML patients with deep molecular responses to TKI have restored immune effectors and decreased suppressors [13]. Taken together, this leads to the concept of combining TKI and IFN-α upfront, to profit from their complementary mode of action (tumor-reduction and immunostimulation).

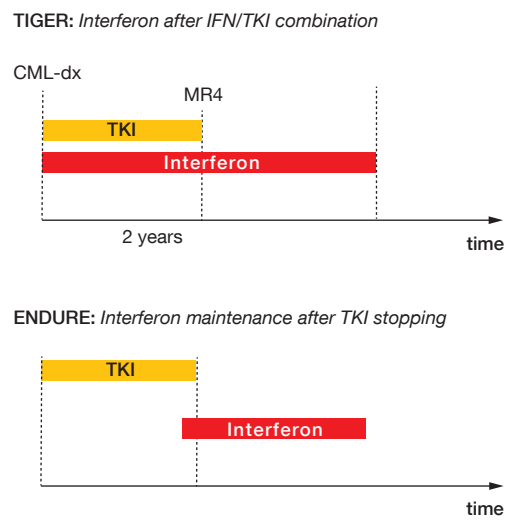

Figure: Design of the TIGER and ENDURE trials

Superior molecular response rates were already observed in two clinical studies combining TKI and IFN-α [14,15], and improved rates of successful TKI discontinuation with prior IFN were observed in a small study [16]. A large multicenter prospective study (TIGER) of nilotinib plus IFN-α followed by IFN-α maintenance in newly diagnosed CML patients is ongoing in Germany, with TFR as the primary endpoint (**Figure**). In addition, the ongoing ENDURE trial is investigating whether maintenance therapy with RopegIFN increases the chances for TFR after stop of TKI monotherapy (**Figure**), to learn whether IFN maintenance is sufficient to improve immune surveillance in CML. ■

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Inflammation in COVID-19 and Similarities with MPN

Prof. Tiziano Barbui (Ospedale Papa Giovanni XXIII, Bergamo) pointed out that overt inflammation plays a major role as reaction to the coronavirus leading to COVID-19. In MPN, subclinical chronic inflammation is linked to the pathogenesis of thrombosis [1].

Indeed, patients with MPN, especially those with ET, carry a high risk of venous thromboembolism during COVID-19 [2], likely due to the inflammatory status following the infection.

Recently, the neutrophil-to-lymphocyte ratio (NLR) has been proposed as a novel predictor of venous thrombosis in MPN [3]. Prof. Barbui presented unpublished data indicating an association between NLR as inflammatory cellular biomarker, the COVID-19 status and the occurrence of thrombosis in MPN patients (**Figure**). Interestingly, increased neutrophil extracellular trap formation has been shown to promote thrombosis in MPN [4], potentially providing a rationale for the increased risk of thrombosis with elevated NLR.

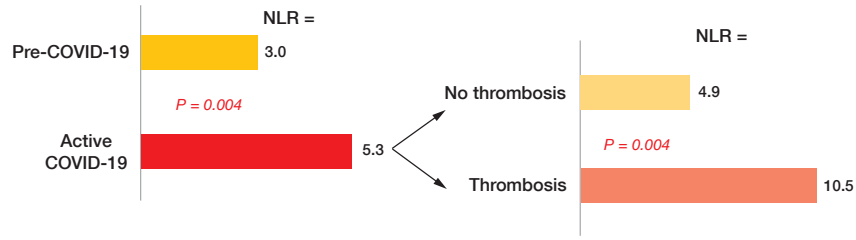

Figure: Neutrophil-to-lymphocyte ratio (NLR) and thrombosis in MPN patients with COVID-19

As concluded by Prof. Barbui, in addition to guiding the stratification of thrombotic risk, these data confirm that inflammation is a relevant target of antithrombotic therapy in MPN. ■

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Other MPN

Pre-PMF – Where are we heading to?

Prefibrotic primary myelofibrosis (pre-PMF) is diagnosed according to WHO criteria by histopathological characterization, plus exclusion of other myeloid neoplasms, plus presence of clonal markers; in addition, at least one of the criteria anemia, leukocytosis, palpable splenomegaly, and LDH increase need to be present [1]. Prof. Heinz Gisslinger (Medical University Vienna) pointed out that overall survival (OS) and leukemia- and myelofibrosis-free survival is shorter in pre-PMF than in ET, while there is no difference in the frequency of thromboembolic events [2].

Histopathology allows to distinguish pre-PMF from ET. Also, the distribution of clinical criteria is different: Anemia, leukocytosis, elevated LDH, splenomegaly, and their combination are significantly more frequent in pre-PMF [3]. Based on this, a diagnostic score for differentiation between pre-PMF and ET has been developed [4]. Moreover, risk stratification in pre-PMF might be important in the planning of clinical studies and in disease management; models have been developed for OS, thrombosis, and bleeding [5-7].

Management of pre-PMF needs to address bleeding and thrombosis, as well as the risk of progression towards overt myelofibrosis. For low risk pre-PMF patients, only observation is recommended; for intermediate risk, symptom driven therapy; for high risk, intense treatment and considering allogeneic SCT [8]. The treatment algorithm in pre-PMF patients with previous thrombosis foresees low dose ASA (if arterial), oral anticoagulation (if venous), and cytoreduction (in the case of thrombocytosis or leukocytosis). If bleeding occurred, ASA needs to be avoided and cytoreduction may be indicated [8].

The first-line cytoreductive treatment used in pre-PMF is HU, but IFN-α may also be a potential treatment option. In a small study, > 80 % of patients derived clinical benefit or stability, and dramatic improvement in marrow morphology occurred in some patients after continuous IFN-α treatment [9]. A Phase 2 study on RopegIFN in pre-PMF was initiated by Prof. Gisslinger: In IFN-naive patients, improvements in blood parameters and most interestingly of LDH levels was observed (**Figure**). In addition to the hematologic response, improved constitutional symptoms and quality of life was noted. Randomized studies are needed to finally define a standard therapy for pre-PMF.

Treatment of myelofibrosis (MF)

A decisional plan for MF therapy needs to start from a proper risk stratification of

patients, as pointed out by Prof. Francesco Passamonti (Università degli Studi dell'Insubria, Varese). For primary MF (PMF), scoring systems like IPSS, DIPPS, or MIPSS-70 [10] should be used, while for post-PV/ET MF the MYSEC prognostic model [11] is appropriate.

Hematopoietic stem cell transplantation (HSCT) is still a central therapeutic option in MF treatment [12], done in 5–10 % of cases. In general, HSCT is considered for patients with a life expectancy of < 5 years. Personalized selection of candidate patients for HSCT can be done, e.g., using DIPPS [13]. Those who might benefit from HSCT can be selected using models to predict transplantation outcome [14,15]. Patients with ongoing spleen response to ruxolitinib before HSCT have the best outcome of transplantation [16]. Splenectomy before HSCT is not associated with OS in general, but advisable in the case of pronounced spleen enlargement [17].

Regarding drug therapy, ruxolitinib is the standard treatment for MF associated splenomegaly [12], achieving spleen response in ~50 % of patients [18]. Early intervention with ruxolitinib seems beneficial [19]. Prof. Passamonti stated that the new standard for second line therapy is fedratinib [20]. Other targeted therapies with the potential to be disease-modifying are under investigation.

Secondary AML

In MPN, the acquisition of additional mutations, including high-risk mutations, may lead to clonal evolution and disease progression and may ultimately culminate in acute myeloid leukemia (AML), also called blast crisis (MPN-BC). In addition, endogenous inflammatory circuits are essential for transformation into MPN-BC. Analysis of *TP53*-heterozygous mutant HSC at different stages of disease evolution revealed that aberrant inflammatory signalling in the genetic ancestors of TP53 "multi-hit" leukemic stem cells, but not the presence of *TP53*-mutations alone, was predictive of subsequent transformation [21].

MPN-BC is a highly aggressive disease with dismal prognosis [22]. Prof. Dominik Wolf (Medical University Innsbruck) stated that the best strategy to prevent blast crisis is to modulate disease-burden during the chronic phase of the disease. In addition, potentially genotoxic drugs, such as hydroxyurea, should be avoided and a pegylated IFN should rather be used early in MPN. If MPN-BC occurs, one needs to consider allogeneic SCT as the only potentially curative approach [23], even though also with SCT survival remains poor.

The genetic landscape in MPN-BC is complex [24]. As stated by Prof. Wolf it is essential to perform targeted next generation sequencing at the point of transformation, to identify mutations that can be exploited for targeted therapy. An example are IDH1/2 mutations occurring in ~20 % of patients; a recent study reported efficacy of ivosidenib and azacitidine in IDH1-mutated AML [25], so this treatment might be considered in MPN-BC as well. If no specific targets are available, a combination of venetoclax/azacytidine or decitabine, chemotherapy, or even a combination of venetoclax and chemotherapy (FLAV-Ida) may be used. The combination of venetoclax and hypomethylating agents resulted in remission rates of 44 % and enabled to proceed to allogeneic SCT in some patients [26]. Cytogenetics and TP53 mutational status rather than degree of cytoreduction are linked to the outcome after SCT in MPN-BC [27].

New compounds

Prof. Jean-Jacques Kiladjian (Université Paris Cité) gave an overview on new drugs under development for MPN:

- There is a need for new treatments of anemia in myelofibrosis. Clinical trials on the erythroid maturation agent luspatercept and the ALK2 inhibitor INCB00928 in patients with myelofibrosis (MF) and anemia are ongoing.

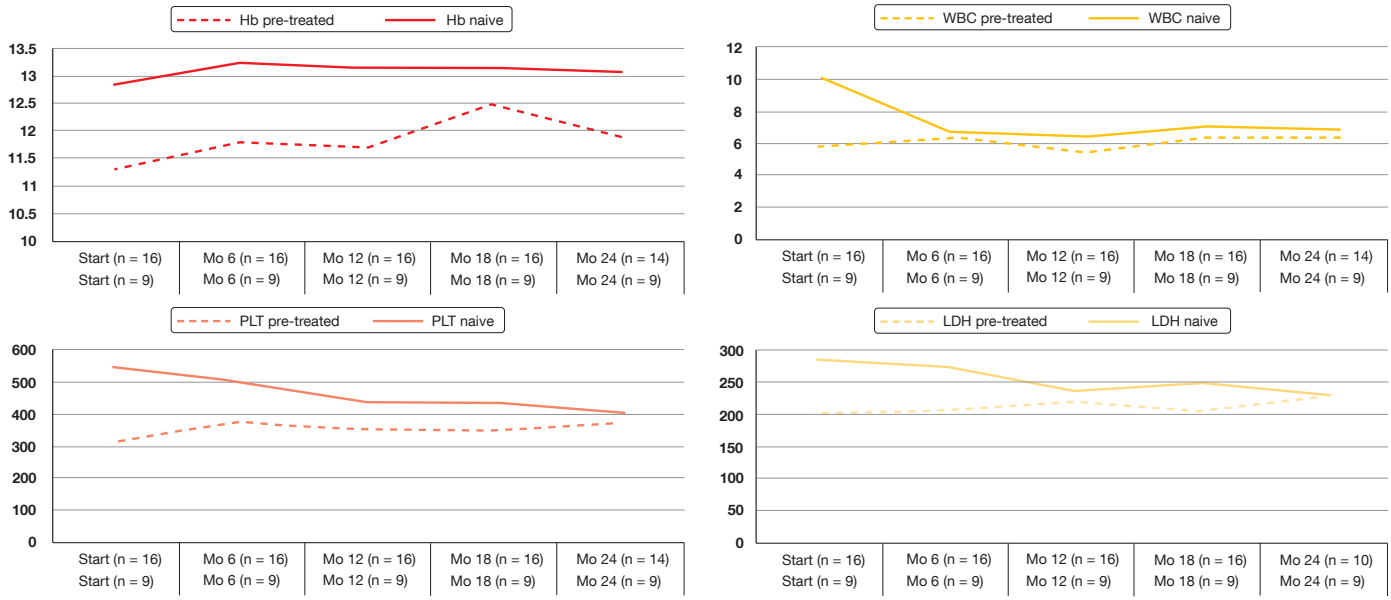

Figure: RopegINF in pre-PMF patients (IASO study): Time course of hemoglobin (Hb), platelets (PLT), WBC, and LDH in pre-treated and treatment naïve patients

- How to improve first-line JAK inhibitor therapy in MF? Three phase-3 clinical trials are studying combination therapy of ruxolitinib with parsaclisib (a selective PI3Kδ inhibitor), navitoclax (an apoptosis inducer), and pelabresib (a BET inhibitor).
- What can be done after ruxolitinib failure in MF? One strategy is to use a different JAK inhibitor, such as fedratinib (EMA/FDA approved), pacritinib (FDA approved), or momelotinib (not approved yet). The choice between these options may depend on the line of treatment and the risk of onset of severe anemia and/or thrombocytopenia [28]. Secondly, combining ruxolitinib with other agents is a possibility; many studies are ongoing in this respect in MF patients, including navitoclax and parsaclisib. Thirdly, a switch to other classes of drugs is investigated in many MF trials; most advanced in clinical development are imetelstat (telomerase inhibitor) and navtemadlin (MDM2 inhibitor).
- New compounds with potential benefit for patients with ET and PV are under development, in particular bomedemstat (an LSD1 inhibitor with highly interesting results in ET patients in a Phase 2 study) [29], and rusfertide (an hepcidin mimetic which in PV patients reduced the need for phlebotomy without inducing iron deficiency) [30]. ■

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