

The EHA Research Roadmap: Malignant Myeloid Diseases

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In 2016, the European Hematology Association (EHA) published the EHA Roadmap for European Hematology Research¹ aiming to highlight achievements in the diagnostics and treatment of blood disorders, and to better inform European policy makers and other stakeholders about the urgent clinical and scientific needs and priorities in the field of hematology. Each section was coordinated by 1–2 section editors who were leading international experts in the field. In the 5 years that have followed, advances in the field of hematology have been plentiful. As such, EHA is pleased to present an updated Research Roadmap, now including 11 sections, each of which will be published separately. The updated EHA Research Roadmap identifies the most urgent priorities in hematology research and clinical science, therefore supporting a more informed, focused, and ideally a more funded future for European hematology research. The 11 EHA Research Roadmap sections include Normal Hematopoiesis; Malignant Lymphoid Diseases; Malignant Myeloid Diseases; Anemias and Related Diseases; Platelet Disorders; Blood Coagulation and Hemostatic Disorders; Transfusion Medicine; Infections in Hematology; Hematopoietic Stem Cell Transplantation; CAR-T and Other Cell-based Immune Therapies; and Gene Therapy.

The malignant myeloid diseases discussed in this section are clonal disorders of hematopoietic stem cells (HSCs) and progenitor cells with various underlying molecular basis, different clinical phenotypes and largely differing prognosis. Although younger patients may be affected, these disorders mainly occur in older individuals, with median ages of patients ranging from 55 to 60 years in chronic myeloid leukemia (CML) to approximately 75 years in myelodysplastic syndromes (MDS). Thus, malignant myeloid disorders represent an increasing burden for healthcare systems in an aging population.

In recent years, major advances have been made in the understanding of the molecular basis of malignant myeloid disorders, in particular with the advent of the next-generation sequencing technologies. European researchers have been leading and were involved in pivotal studies deciphering single disease genes, such

as JAK2 or CALR mutations in myeloproliferative neoplasms (MPNs) or entire molecular disease landscapes. Recent studies have provided evidence that some of these gene mutations associated with malignant myeloid disease are commonly acquired in HSCs during aging, a phenomenon that was termed “clonal hematopoiesis of indeterminate potential” (CHIP) or “age-related clonal hematopoiesis” (ARCH). CHIP has been associated with malignant myeloid diseases, but also with an increased risk of cardiovascular diseases and decreased overall survival.

The better understanding of the molecular basis has paved the way for precision medicine approaches in malignant myeloid disorders. This is exemplified by the successful development of FLT3-, IDH1/IDH2-, or BCL-2 inhibitors in acute myeloid leukemia (AML), of next-generation tyrosine kinase inhibitors in CML, or of JAK2-inhibitors in MPN. European research in

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hematology has a long-standing tradition of well-organized clinical trial groups conducting well-designed pivotal phase 3 studies, thereby making major contributions to this development.

Under the umbrella of the European LeukemiaNet (ELN) and the European Hematology Association (EHA), European researchers—in collaboration with other international experts—have published a wealth of recommendations and guideline papers that have been highly valuable for the scientific community, patients, care givers, and also for regulatory authorities.

Nevertheless, major challenges remain in improving outcomes and quality of life for patients with malignant myeloid diseases. One challenge relates to the enormous (epi-)genomic complexity of most of these disorders, with multiple epigenetic lesions being present at diagnosis, and subsequent clonal evolution over the disease course with various mechanisms of resistance. Thus, overcoming primary and/or secondary resistance to conventional as well as targeted agents will be a major task in this Research Roadmap. Another hurdle relates to challenges in future clinical trial design. Malignant myeloid disorders in general are rare diseases, and with the development of precision medicine in molecular subgroups, the conduct of pivotal phase 3 studies has become challenging. Thus, a joint European and intercontinental effort—in close collaboration with important stakeholders such as patient advocacy groups, biotech and pharmaceutical industry—will be necessary to expedite the development of new therapies for our patients.

MDSs and myelodysplastic/MPNs

Introduction

The MDSs are clonal disorders of HSC which are characterized by peripheral blood cytopenia, dysplasia in one or more myeloid cell lines, and a propensity to evolve into AML. Myelodysplasia is not restricted to MDS but may be found also in other myeloid neoplasms, in particular in the so-called MDS/MPN, which mainly include chronic myelomonocytic leukemia and less frequent diseases, including atypical CML, chronic neutrophilic leukemia, juvenile myelomonocytic leukemia, MDS/MPN with ring sideroblasts, and thrombocytosis.

The crude incidence rate of MDS is 4 per 100,000 people per year, but increases up to 50 per 100,000 persons per year over the age of 60, indicating that >30,000 new cases are expected in Europe each year and making MDS one of the most common hematologic malignancies in Western countries. Furthermore, recent data suggest that this incidence may be significantly underestimated, because many MDS patients may remain underdiagnosed as anemia or cytopenia of the elderly.

MDSs are caused by somatic mutations that occur in HSC, conferring a proliferative advantage to HSC while inducing ineffective differentiation and maturation of hematopoietic progenitor cells resulting in peripheral blood cytopenia.^{2–6} Recent studies provided evidence that somatic mutations in some of the genes frequently mutated in MDS are commonly acquired in HSC during aging, and that apparently normal subjects with these mutations have increased risk of hematologic malignancies and increased cardiovascular and all-cause mortality (ARCH or CHIP).

MDS and MDS/MPN show marked clinical heterogeneity, ranging from conditions with an indolent clinical course and a near-normal life expectancy to entities with very poor prognosis. A risk-adapted treatment strategy is therefore mandatory for these disorders. At present, the only treatment with a potentially curative effect is allogeneic HSC transplantation (HSCT). Azacitidine can prolong survival in patients with high-risk MDS, while erythropoiesis-stimulating agents and lenalidomide improve anemia in patients with low-risk MDS and the MDS

associated with deletion 5q, respectively.^{7,8} More recently, luspatercept has been proven effective in reducing transfusion burden in MDS with ring sideroblasts.⁹ Chronic red cell transfusion remains the mainstay of therapy for many patients with MDS.

European research contributions

In the past few years, major advances in the understanding of the genetic basis of MDS have been made by means of massive parallel DNA sequencing, and a number of seminal studies have been performed in Europe.^{2–6}

Approximately, 90% of MDS patients carry one or more oncogenic mutations with two-thirds of them are found in individuals with a normal karyotype. Driver mutations have been identified in genes involved in RNA splicing, DNA methylation, chromatin modification, transcription regulation, DNA repair, and signal transduction. Only a few genes are consistently mutated in 10% or more MDS patients, including those involved in epigenetic regulation (*TET2*, *ASXL1*, and *DNMT3A*) and splicing factors (*SF3B1*, *SRSF2*, and *U2AF1*), while a long tail of >50 genes are mutated less frequently.^{3,4} Mutations in *SF3B1* have been found to be highly specific for MDS with ring sideroblasts and are associated with a very low risk of disease progression and a favorable outcome.⁵

European hematologists have provided pivotal contributions to developing effective treatments for MDS, including erythropoietin, azacitidine, lenalidomide, and luspatercept.^{7–9} Recommendations for treatment of the individual patient with MDS, including allogeneic HSCT, have also been developed in recent years.^{10–12}

Seminal contributions have also been made in pediatric hematology, for example, in elucidating the genetic predisposition to juvenile myelomonocytic leukemia, as well as to MDS or other myeloid neoplasms.¹³

Proposed research for the Roadmap

Myeloid malignancies appear to be propagated by rare self-renewing mutant HSCs. However, the cellular and molecular mechanisms that regulate development, propagation, and therapy resistance of these myelodysplastic stem cells remain unknown. Studies are needed to:

1. characterize cellular and molecular mechanisms involved in disease development, progression and therapy resistance, including germline predisposition, chronic inflammation, microenvironmental and immunological abnormalities, as well as immune escape following stem cell transplantation;
2. identify premalignant conditions associated with increased risk to develop MDS and MDS/MPN and recognize the interaction of hematopoietic clones with multimorbidities and complex chronic conditions in older persons;
3. identify therapeutic targets for efficient elimination of the MDS-propagating cells and establish suitable frameworks for biology-driven clinical trials.

While recent advances have shed light on the genetic complexity of MDS paving the way for precision medicine strategies, the factors enabling the emergence, selection, and subsequent leukemic evolution of these clones remain incompletely understood. Single-cell studies combining analysis of the genome and transcriptome as well as preclinical models are warranted to identify the impact of recurrent molecular abnormalities on gene expression, to detect the deviation of mutant cells from their normal counterpart, and to identify mesenchymal niche abnormalities and disrupted signaling contributing to the occurrence of somatic mutations, their selection, and subsequent clonal expansion.¹⁴ Systematic studies of comprehensive mutational profiling of germline and somatic mutations within the frame

of population-based registries and clinical trials are required to define the clinical implications of mutation profiles in unbiased and homogeneously treated patient populations.

Studies aimed at characterizing CHIP and identifying intra-clonal and extraclonal variables associated with progression into overt malignancy are required and will pave the way to early diagnosis and pre-emptive interventions. Emerging data are pointing toward a strong interaction of myelodysplastic clones with age-related chronic inflammation, as well as with multimorbidities and complex chronic conditions. Population-based studies that analyze the relationships between clonal hematopoiesis and its genetic drivers, gender, age, and comorbidities are needed.

Outcome improvements in MDS patients remain modest. Identifying therapeutic agents that may further improve survival and quality of life of patients with MDS represents a priority. Promising strategies include combination treatment containing azacitidine in high-risk MDS (including BCL-2 inhibitors), and drugs that inhibit ineffective erythropoiesis and improve anemia in those with low-risk MDS. Novel drugs targeting molecular abnormalities, including spliceosome, epigenetic regulators (particularly IDH1 and IDH2), and *TP53* mutations, are currently under investigation and should be further developed. Establishing suitable frames for biology-driven clinical trials is needed, and patient inclusion in clinical trials should be encouraged. Reducing the toxicity of allogeneic HSCT in MDS and MDS/MPN elderly population will be critical to allow more patients to benefit from the procedure. More effective transplantation procedures integrating biology-driven pretransplant and posttransplant should be developed.

Anticipated impact of research

The current lack of understanding the molecular mechanisms that regulate MDS stem cell expansion and their escape from therapeutic and immunological targeting is limiting our ability to efficiently eradicate these disorders. The research lines described above have the potential to decipher these mechanisms and identify suitable targets for effective intervention.

The identification of premalignant conditions with no or mild clinical expressivity will allow to develop effective strategies of early diagnosis and intervention aimed at preventing clonal expansion and progression.

The characterization of genomic and transcriptomic profiles of each individual patient with MDS or MDS/MPN will allow the most appropriate treatment to be selected, patients to be enrolled in ad hoc clinical trials investigating new targeted therapeutic agents, and molecular biomarkers for monitoring response to treatment to be identified. This will eventually lead to precision medicine strategies.

Acute myeloid leukemia

Introduction

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults with an estimated incidence of 3.7 per 100,000 individuals, resulting in 17,000 newly diagnosed patients each year in Europe. The incidence rises with age (median age is 70 y) implicating a further rise in future years.¹⁵ This is a clonal disorder arising from hematopoietic progenitor cells characterized by defects in their maturation program resulting in uncontrolled proliferation and subsequent bone marrow failure. Genomic techniques have unraveled the molecular complexity of AML that guided refinement of risk stratification and personalized therapeutic strategies for AML patients.^{16,17} The prognosis is poor with cure rates of 40%–50% in the younger population decreasing to <10%–15% in the

elderly. Until recently, therapeutic options were mostly limited to cytotoxic chemotherapy. Increased donor availability coupled with the advent of reduced intensity conditioning regimens has led to allogeneic HSCT becoming an increasingly important potentially curative treatment strategy.¹⁸

However, there has been an explosion of newly approved drugs since 2017, with the majority of them targeting specific gene mutations and/or pivotal cell survival pathways.¹⁹ These novel agents have been tested mainly in older patients with comorbidities and/or relapsed/refractory disease, in whom the treatment of choice is limited and the clinical outcome is very poor. Recently, the combination of venetoclax and azacitidine (Ven/Aza) has been shown to improve survival in elderly AML patients.²⁰ At the same time, increased donor availability coupled with the advent of reduced intensity conditioning regimens has led to allogeneic HSCT becoming an increasingly important potentially curative treatment strategy.¹⁸

European research contributions

Europe has a longstanding tradition in performing well-designed phase 3 studies by experienced and well-organized AML trial groups. Until recently, these studies were mainly performed in all comers investigating new drugs in combination with the 3+7 backbone already standard of care for decades. Reduced intensity conditioning regimens, graft-versus-host disease prophylaxis and posttransplant interventions in allogeneic HSCT all have contributed to the better outcome of AML. Now since druggable genetic biomarkers are identified and new targeted drugs have become available, more targeted trials will be conducted.¹⁹ Given this segregation, collaboration between European trial groups are required if the delivery of practice informing trials of new drug and transplant therapies is to be accelerated. Already a combined effort of European trial groups has resulted in the approval of a drug targeting CD33: Gemtuzumab Ozogamycin.²¹ Another major achievement is the successful development of a chemotherapy-free regimen in acute promyelocytic leukemia (APL) with cure rates >95% in low- and intermediate-risk APL.²²

The internationally embraced ELN recommendations on the diagnosis and management of AML now plays a pivotal role in the management of AML internationally having transformed clinical practice.¹⁸ The European concept of the assessment of measurable residual disease (MRD) has significantly improved the management of AML. The ELN recommendation on MRD plays an important role in harmonization and standardization of flow cytometric and molecular techniques for MRD monitoring, resulted in the development of new clinical guidelines and informed decision making by regulatory authorities including the FDA and EMA.²³

New insights in the biology of AML with mutated, translocated, or overexpressed genes, like *NPM1*, *PML-RARA*, *CEBPA*, *MECOM (EV11)*, and germ-like mutations, predisposing to the development of AML have been identified by European investigators.¹⁷

Proposed research for the Roadmap

Collaboration between basic, translational, and clinical hematologists will be required to generate continuous major progress in the next years.

Given the molecular heterogeneity underlying AML, large cohorts need to be analyzed to better capture how genetic aberrations can affect treatment outcome.¹⁶ Within the HARMONY Alliance, a large pan-European public-private partnership funded through the Innovative Medicines Initiative (IMI), a large “Big Data for Better Outcome” platform for AML has been built with the aim to put together at least 10,000 cases

of AML (<https://www.harmony-alliance.eu/>). Gene–gene interactions analysis will detect new patterns of co-occurrence and mutual exclusivity and correlation with clinical outcome will provide significant information on treatment and course of the disease. Genomic analysis of single cells will lead to a better understanding of the multiclonal diversity of AML at diagnosis and during evolution.²⁴

Further standardization and development of MRD techniques to increase sensitivity, making use of peripheral blood instead of bone marrow, automatic analysis, is work in progress in the ELN MRD Working Party.²³ Apart from the already established value of diagnosis next-generation sequencing should additionally be explored for MRD detection; here, gene panels will also allow to further elucidating clonal evolution and resistance in serial analysis.²⁵ In addition, studies to convert MRD positivity to negativity pretransplant have to be done as well as studies addressing the question that MRD apart from prognostic value also has predictive value in order to be accepted as surrogate for survival.²⁶

Certain genetic and molecular defined AMLs (eg, *TP53*^{mut}, monosomal karyotype, *ASXL1*^{mut}, and *RUNX1*^{mut}) are associated with a poor prognosis.¹⁶ New therapeutic strategies/drugs should be investigated in these AML subtypes. Also AMLs with druggable mutations (eg, *FLT3*^{mut} and *IDH*^{mut}) should be investigated in separate trials either by adding new drugs to a 7+3 backbone or in combinations or triplets based on the good results with the combination Ven/Aza.^{20,27} Because these are only small subgroups, these research questions only can be accomplished by collaborations between all the major trial groups in Europe. Because relapse after transplantation is still an important cause of failure after the most effective antileukemic treatment, strategies to reduce the risk of relapse rate posttransplantation are urgently needed and are currently being examined through prospective randomized trials led by European groups.

The role of maintenance treatment should be explored. Recently, CC-486, an oral hypomethylating agent, applied as maintenance has been shown to improve overall survival in elderly patients in CR/CRi not suitable for transplantation.²⁸ Maintenance treatment should be studied by appropriate delivery of immunotherapy, hypomethylating agents, and targeted small molecules in remission.

The promising impact of immunotherapy (eg, armed antibodies, bispecific antibodies, vaccines, immune checkpoint inhibitors, and CAR-T cells) should be intensively explored.

At the same time, we need a better understanding of mechanisms of leukemic stem/progenitor resistance to classical chemotherapy and targeted agents, an area where European scientific programs excel. A better understanding and characterization of leukemic stem/progenitor cells, the impact of the clonal architecture of leukemia, and the clonal evolution during the disease course should pave the way to target them.

Finally, we are now improving not only curing patients but also extending survival without cure. Quality of life issues have been neglected in AML, and have more recently become more and more relevant and should become part of our research agenda and each clinical trial.

Anticipated impact of the research

The proposed research aims at further deciphering the complex molecular heterogeneity of myeloid diseases, which ultimately will result in further refinement of this disease. Big data mining will be instrumental for detecting gene–gene interactions, performing automatic analysis of MRD and developing personalized treatment.

The heterogenous clonal architecture of the disease suggests that most likely no single drug is expected to cure AML. Rather, the combination of classical standard chemotherapy with novel agents or combinations of novel agents are expected to improve the

outcome. Accelerated delivery of prospective transplant trials will also provide insights into strategies to improve transplant outcome. Special attention must also be paid to the better management of older patients, given the more unfavorable and distinct biology and the still dismal outcome of the disease in these patients.

The proposed research directions are expected to provide major contributions to improving outcome in patients with this fatal disease.

Chronic myeloid leukemia

Introduction

Chronic myeloid leukemia (CML) is a neoplastic disease of HSCs. CML is typically linked to the Philadelphia Chromosome, a shortened chromosome 22 as the result of a reciprocal translocation of chromosomes 9 and 22 leading to fusion of *BCR* and *ABL1* genes. CML constitutes about 15% of all leukemias and occurs with an incidence of about 1.2/100,000. CML went along with an almost fatal outcome until 20 years ago. Through the excellent results of BCR-ABL1 tyrosine kinase inhibitor (TKI) treatment, most CML patients face an excellent prognosis.^{29–31} Currently, about 10%–20% of patients will achieve a condition of treatment-free remission (TFR). The use of interferon alpha (IFN) in parallel with or after TKI therapy could be associated with the induction of an immune response against the leukemic clone with further improvement of the remission rate. The essential part of the management of CML patients is a rigorous use of standardized surveillance methods to regularly assess the residual disease status. Adverse events should be prevented by individual selection of therapy according to patients' risk profiles. Patients' advocacy groups have become partner organizations in education, clinical practice and research. Prevalence of patients with CML treated with TKIs is steadily increasing, which is a challenge for healthcare systems worldwide. The main task is to optimize treatment for patients' maximum benefit with an affordable allocation of the resources.

European research contributions

European cooperative CML study groups have been established 30–40 years ago and have continuously contributed to the optimization of management. The impact of IFN has been investigated in a series of large studies. IFN as an immunomodulatory agent has activity in CML and has resulted in sustained cytogenetic remissions in an important minority of patients.²⁹ Meta-analyses between conflicting studies revealed new prognostic factors for IFN response. The place of allogeneic HSCT in disease management had been gradually evolving, having been displaced as the first-line treatment by 2002, and then moving to a third or fourth line option after the licensing of the second-generation TKIs in 2006. From 2001, European investigators have participated in the clinical development of 6 TKIs. National and multinational (ELN) networks of European CML investigators and clinicians have produced fundamental knowledge for clinical practice.^{31–34} Cooperative studies have contributed to the understanding of the biology of TKI response. In addition, the impact of combination therapies and baseline and time dependent prognostic factors contributed. As a result of a study of the ELN involving >5000 patients, a new score predicting the CML-specific survival on TKI therapy was established.³² The predictive value of early molecular response, deep molecular response, and the velocity of response has been identified in Europe. ELN expert recommendations for CML management published in 2006, 2009, 2013, and 2020 and have become a key reference for CML treatment worldwide.³¹

In basic and translational research, European investigators significantly contributed to the understanding of the mechanisms

of TKI resistance and how to prevent and overcome it.³⁴ Molecular monitoring of CML has been developed, optimized, and standardized in Europe, allowing accurate quantification of residual disease in a dynamic range of 6 orders of magnitude. Such contribution permitted the successful attempt to discontinue treatment after deep molecular response.^{33,35} Currently, biology of persistence of BCR-ABL1 positive stem cells has been a major focus of research. Other research directions include the origin of CML, the clonal molecular evolution, and the characterization of the BCR-ABL1 negative hematopoiesis.

Proposed research for the Roadmap

TKIs have substantially improved the survival of CML patients. There is reasonable expectancy to cure the disease in a significant proportion of patients. The main objective is to integrate the leading European national trial groups in CML to form a cooperative network for advancements in CML related research and health care. Within the group of European Investigators on CML (EICML), a clinical trials platform was created to promote the performance of clinical trials with new drugs and/or treatment strategies. Standardization of diagnostic and therapeutic procedures allows outcome comparison across Europe. We aim to improve (1) tolerability of the treatment; (2) the rate of deep molecular response; and (3) the rate of patients in durable remission after stopping TKI. Enhanced inhibition of BCR-ABL1 with more specific inhibitors or drug combinations are possible strategies to improve TFR by increasing the rates of deep molecular response.³⁶ Clinical approaches utilizing immune surveillance to eradicate residual leukemic cells are potential future research directions to improve TFR rates. Despite major improvement in the standard of care for CML, the complexity of CML blast crisis pathophysiology, together with the failure of TKIs to eradicate CML at the stem cell level, as well as the observation of molecularly defined BCR-ABL1 negative clones demand further research. A better understanding of the events governing leukemic stem cell behavior might lead to the biological cure of CML and effective treatment of blast crisis. Current efforts continue to uncover new pathways involved in BCR-ABL1 independent TKI resistance. Inhibition of BCL2 and MEK, for example, both showed promise in preclinical models awaiting and testing in clinical trials. Translational studies will contribute to early outcome prediction and treatment surveillance. Establishing preclinical models that more faithfully reflect human CML and its progression to blast phase, along with simplifying clinical trials will also be critical for progress in this area. Biostatisticians and patient advocacy groups cooperate with the study groups with a European clinical trials platform which will support the coordination of the studies.

Research Agenda:

- Increasing the rate of TFR;
- Overcoming TKI resistance in patients with multi-TKI failure;
- Improving outcomes for patients with accelerated and blast phase CML;
- Developing better animal models that more faithfully recapitulate features of human CML;
- Preventing cardiovascular toxicity associated with second- and third-generation TKIs.

Anticipated impact of research

A more in-depth molecular and cellular characterization of CML patients might facilitate personalized medicine regarding diagnosis, prognostication, and therapeutic decisions. Overall, this will have a major impact in lowering the disease burden, reducing the rate of complications and, prospectively,

prolonging survival. The cost of novel technologies and treatments might be balanced by their more specific application as well as a favorable impact on the patients' quality of life and the lessened burden for caregivers; this will translate into a more general favorable impact for the society in general by reducing use of resources and improving individual work capabilities. Standardization of diagnostics and therapeutic procedures will further strengthen integration. The thereby achieved comparability of outcome will facilitate recognition of interstudy differences and rare subtypes. Recommendations, network meetings, training courses, and exchange of researchers will spread excellence and raise standards of research and patient care across Europe. The CML network and its activities provide the critical mass for added value and European leadership. The impact on the future management of CML patients is expected to be considerable, since a rational advanced treatment design will likely lead to higher remission rates, longer survival and a higher proportion of patients in which treatment can be permanently discontinued as an indicator of cure.

Myeloproliferative neoplasms

Introduction

The MPNs are disorders of HSC, and include polycythemia vera (PV), essential thrombocythemia (ET), prefibrotic and overt primary (PMF), and post-PV/post-ET myelofibrosis. These are chronic disorders usually affecting middle-aged patients; however, younger patients are now more frequently diagnosed thanks to greater awareness and broad availability of assays for MPN-associated driver mutations (*JAK2V617F*, *JAK2* exon12, *MPL*, and *CALR* mutation). The estimated annual incidence rate of MPN in RARECAREnet registry (<http://www.rarecarenet.eu>) is 2.17 cases $\times 10^5$ /year; prevalence remains difficult to determine, but it is likely raising owing to improved management. MPN remain incurable diseases. While many patients with ET and PV display survival similar to control population, median survival in PMF is 6 years, although it may be improving following the introduction of ruxolitinib as standard of care. MPN patients suffer from major thrombotic events and hemorrhages. Quality of life is often impaired, most frequently in MF, due to a hyperinflammatory condition, responsible for disabling constitutional symptoms, and due to clonal cell proliferation that causes cytosis, hepatosplenomegaly and extramedullary hematopoiesis. A rapidly fatal, therapy-refractory, acute leukemia may develop in up to 15%–20% of all MPN.

European research contributions

The contribution of European scientists to basic, translational and clinical research is long standing and valuable. European researchers made the breakthrough discoveries of the *JAK2V617F*, *JAK2* exon 12, and *CALR* mutations, which radically modified the understanding of MPN pathophysiology and revolutionized the WHO diagnostic criteria, to which European hemopathologists gave substantial contributions. Genetic haplotypes predisposing to MPN were primarily discovered in Europe. The prognostic impact of driver and subclonal mutations in MF was described by European researchers, in collaboration with American colleagues, and promoted the development of new disease classification criteria and risk scores such as the MIPSS-70 score for PMF,³⁷ the MySEC-PM score for secondary MF,³⁸ the MTSS score for MF patients undergoing HSCT,³⁹ and an integrated genomic score for all MPN.⁴⁰ The IPSS and DIPSS score for MF were also products of research mostly done in Europe. European researchers were deeply involved in pivotal studies leading to the approval of the JAK1 and JAK2 inhibitors ruxolitinib and fedratinib,^{41–43} and more recently of ropeg-interferon in PV⁴⁴; several other ongoing clinical trials exploring

novel targeted therapies are led in Europe. Notably, fundamental studies conducted in Europe, that established new paradigms of clinical management, were investigator-initiated trials, such as: the ECLAP study, on low-dose aspirin in PV; the CytoPV trial, that established the optimal hematocrit target in PV; the PT-1 and the ANAHYDRET study, that compared hydroxyurea versus anagrelide for high-risk ET patients; a prospective comparison of hydroxyurea plus aspirin with aspirin alone in younger patients with low-risk ET⁴⁵; the low-PV trial with ropeg-interferon in low-risk PV. European researchers active in the MPN field refer to several national and supra-national (the ELN) networks that have produced popular guidelines, expert opinions, drug intolerance/resistance and treatment response criteria, and endpoints for novel drug studies.⁴⁶ An European initiative (E-MPN network) connecting major centers involved in translational and clinical research has been launched recently with the aim to generate large bio-registries/biobanks. Strong, productive partnerships between European researchers and excellence research and clinical centers outside Europe, particularly in the United States, are well established.

Proposed research for the Roadmap

Fundamental questions on the molecular architecture of MPN remain unanswered: in about 20% of patients with ET and PMF the disease-initiating mutation remains unknown (“triple negative” patients); the relationships between the phenotype-driver mutations and additional somatic mutations need to be defined in more detail (impact of the order of events); the genetic basis for familial clustering of MPN and, above all, the genetic events that underlie transformation of chronic MPN to aggressive acute leukemia need to be fully understood. Use of novel, high-throughput, single-cell platforms, coupled with massive sequencing of noncoding regions, DNA methylation profiling, proteomic studies, targeted gene manipulation, and PDX, humanized animal models, will contribute to advancing our knowledge of MPN pathophysiology. Results from these basic/translational studies are predicted to have rapid and valuable impact on diagnosis, risk stratification, and novel therapeutic developments. We need criteria for categorizing patients, especially MF, according to their response to novel therapies, to identify those who have the greatest chance to benefit from one drug, or drug combination, or conversely have poor or short-term responses, and/or suffer from toxicities, thereby allowing early shift to alternatives. Since the JAK inhibitors are not curative, better understanding of clonal cells’ abnormalities, cell-autonomous and microenvironment-directed signals, and host unique genomic signature, might all facilitate discovery of novel targets. Strategies to develop early interventions and possibly preventive measures in asymptomatic carriers of MPN-driven mutations (CHIP) need to be explored. Entirely new therapeutic approaches, including monoclonal antibodies and antigen-activated immune cells, are also worthwhile of being explored. Treatment of post-MPN acute leukemia represents an urgent unmet need. Preclinical and clinical studies might be fostered by reinforcing the existing networks of European researchers to share annotated patients’ samples, take advantage of new technologies and expertise, and facilitate patient referral for phase 1/2 clinical trials.

Anticipated impact of research

The great advances in understanding and managing MPN that happened in the last decade had profound impact on the patients’ journey, opened new avenues in cell and molecular biology and promoted the development of an entirely new class of agents as are the JAK inhibitors, that are finding unanticipated roles in diseases far from MPN, such as the graft-versus-host disease, autoimmune disorders and possibly COVID-19.^{47,48} The next steps are to use insights from population-derived studies to develop

Summary box: Main research & policy priorities

1. Deeper understanding of the role of CHIP for the development of overt myeloid malignancies and other age-related chronic conditions.
2. Further deciphering of the genetic and epigenetic complexity of malignant myeloid disorders.
3. Identification of new therapeutic targets and development of new precision medicine strategies.
4. Overcoming primary and/or secondary resistance to conventional as well as molecular-targeted agents.
5. Harmonization and standardization of existing and emerging techniques for the assessment of MRD.

concepts and approaches for personalized medicine approach, ranging from refined diagnostic categories to alternative therapies based on prediction of the individual benefit/risk ratio. This will not only impact favorably on the diseased individual, but may strengthen the relationships between European academy and the industry by fostering pharmaceutical research, and positively impact on patients’ families and the society in general by optimizing use of resources and improving individual work capabilities.

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References

1. Engert A, Balduini C, Brand A, et al. The European Hematology Association Roadmap for European Hematology Research: a consensus document. *Haematologica*. 2016;101:115–208.

2. Delhommeau F, Dupont S, Della Valle V, et al. Mutation in TET2 in myeloid cancers. *N Engl J Med*. 2009;360:2289–2301.
3. Papaemmanuil E, Cazzola M, Boultonwood J, et al. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *N Engl J Med*. 2011;365:1384–1395.
4. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood*. 2013;122:3616–3627.
5. Malcovati L, Stevenson K, Papaemmanuil E, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. *Blood*. 2020;136:157–170.
6. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat Med*. 2020;26:1549–1556.
7. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*. 2009;10:223–232.
8. Jädersten M, Malcovati L, Dybedal I, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. *J Clin Oncol*. 2008;26:3607–3613.
9. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med*. 2020;382:140–151.
10. Malcovati L, Hellström-Lindberg E, Bowen D, et al. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood*. 2013;122:2943–2964.
11. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood*. 2017;129:1753–1762.
12. Itzykson R, Fenaux P, Bowen D, et al. Diagnosis and treatment of chronic myelomonocytic leukemias in adults: recommendations from the European Hematology Association and the European LeukemiaNet. *HemaSphere*. 2018;2:e150.
13. Niemeyer CM, Kang MW, Shin DH, et al. Germline CBL mutations cause developmental abnormalities and predispose to juvenile myelomonocytic leukemia. *Nat Genet*. 2010;42:794–800.
14. Rodriguez-Meira A, Buck G, Clark SA, et al. Unravelling intratumoral heterogeneity through high-sensitivity single-cell mutational analysis and parallel RNA sequencing. *Mol Cell*. 2019;73:1292–1305.e8.
15. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373:1136–1152.
16. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374:2209–2221.
17. Bullinger L, Döhner K, Döhner H. Genomics of acute myeloid leukemia diagnosis and pathways. *J Clin Oncol*. 2017;35:934–946.
18. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–447.
19. Döhner H, Wei A, Löwenberg B. Towards precision medicine for AML. *Nat Rev Clin Oncol*. 2021 May 18. [Epub ahead of print].
20. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383:617–629.
21. Lambert J, Pautas C, Terré C, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. *Haematologica*. 2019;104:113–119.
22. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *N Engl J Med*. 2013;369:111–121.
23. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood*. 2018;131:1275–1291.
24. Potter N, Miraki-Moud F, Ermini L, et al. Single cell analysis of clonal architecture in acute myeloid leukaemia. *Leukemia*. 2019;33:1113–1123.
25. Jongen-Lavrencic M, Grob T, Hanekamp D, et al. Molecular minimal residual disease in acute myeloid leukemia. *N Engl J Med*. 2018;378:1189–1199.
26. Thol F, Gabdoulline R, Liebich A, et al. Measurable residual disease monitoring by NGS before allogeneic hematopoietic cell transplantation in AML. *Blood*. 2018;132:1703–1713.
27. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377:454–464.
28. Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383:2526–2537.
29. Hehlmann R, Lauseker M, Sauße S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. *Leukemia*. 2017;31:2398–2406.
30. Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med*. 2017;376:917–927.
31. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34:966–984.
32. Pfirrmann M, Clark RE, Prejzner W, et al. The EUTOS long-term survival (ELTS) score is superior to the Sokal score for predicting survival in chronic myeloid leukemia. *Leukemia*. 2020;34:2138–2149.
33. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19:747–757.
34. Hehlmann R, Voskanyan A, Lauseker M, et al. High-risk additional chromosomal abnormalities at low blast counts herald death by CML. *Leukemia*. 2020;34:2074–2086.
35. Sharf G, Marin C, Bradley JA, et al. Treatment-free remission in chronic myeloid leukemia: the patient perspective and areas of unmet needs. *Leukemia*. 2020;34:2102–2112.
36. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. *N Engl J Med*. 2019;381:2315–2326.
37. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: mutation-enhanced international prognostic score system for transplantation-age patients with primary myelofibrosis. *J Clin Oncol*. 2018;36:310–318.
38. Passamonti F, Giorgino T, Mora B, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. *Leukemia*. 2017;31:2726–2731.
39. Gagalman N, Ditschkowski M, Bogdanov R, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. *Blood*. 2019;133:2233–2242.
40. Grinfeld J, Nangalia J, Baxter EJ, et al. Classification and personalized prognosis in myeloproliferative neoplasms. *N Engl J Med*. 2018;379:1416–1430.
41. Harrison C, Kiladjan JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366:787–798.
42. Vannucchi AM, Kiladjan JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372:426–435.
43. Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. *Lancet Haematol*. 2017;4:e317–e324.
44. Gisslinger H, Klade C, Georgiev P, et al. Ropeninterferon alfa-2b versus standard therapy for polycythemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. *Lancet Haematol*. 2020;7:e196–e208.
45. Godfrey AL, Campbell PJ, MacLean C, et al. Hydroxycarbamide plus aspirin versus aspirin alone in patients with essential thrombocythemia age 40 to 59 years without high-risk features. *J Clin Oncol*. 2018;36:3361–3369.
46. Barbui T, Tefferi A, Vannucchi AM, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia*. 2018;32:1057–1069.
47. Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for glucocorticoid-refractory chronic graft-versus-host disease. *N Engl J Med*. 2021;385:228–238.
48. Vannucchi AM, Sordi B, Morettini A, et al. Compassionate use of JAK1/2 inhibitor ruxolitinib for severe COVID-19: a prospective observational study. *Leukemia*. 2021;35:1121–1133.