Leukemia Research 35 (2011) 291–294

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Meeting report

Aplastic Anemia & MDS International Foundation (AA&MDSIF): Bone Marrow Failure Disease Scientific Symposium 2010

Luca Malcovati[a,1], Régis Peffault de Latour[b,*,1], Antonio Risitano[c,1]

[a] Department of Hematology Oncology, Fondazione IRCCS Policlinico S. Matteo, University of Pavia, Pavia, Italy
[b] Service d'Hématologie Greffe, Hôpital Saint Louis, 1 Avenue Claude Vellefaux, Paris, France
[c] Hematology, Department of Biochemistry and Medical Biotechnology, Federico II University of Naples, Naples, Italy

ARTICLE INFO

Article history:
Received 1 October 2010
Received in revised form 3 October 2010
Accepted 11 October 2010
Available online 30 October 2010

Keywords:
Myelodysplastic syndromes
Aplastic anemia
Paroxysmal nocturnal hemoglobinuria
Bone marrow failure
Epigenetic therapy
Immunosuppressive therapy
Stem cell transplantation
Complement

ABSTRACT

Aplastic anemia (AA) and myelodysplastic syndromes (MDS) are a heterogeneous group of rare hematological disorders belonging to the Bone Marrow Failure (BMF) syndromes. The Aplastic Anemia and Myelodysplastic Syndromes International Foundation (AA&MDSIF) is a non-profit organization dedicated to supporting patients and families living with a BMF disease. They work to bring investigators together in a collaborative manner. This article summarizes key presentations from the last AA&MDSIF scientific symposium held in Bethesda, Maryland on March 2010.

1. Introduction

Bone marrow failure (BMF) syndromes are a heterogeneous group of rare hematological disorders characterized by the impairment of hematopoiesis. The spectrum of primary BMFS includes both constitutional and acquired forms, which harbor specific clinical presentations and pathogenic mechanisms. The Aplastic Anemia and MDS International Foundation (AA&MDSIF) is a non-profit organization dedicated to supporting patients and families living with a BMF disorder, including aplastic anemia (AA), myelodysplastic syndromes (MDS), paroxysmal nocturnal hemoglobinuria (PNH), or related BMF diseases. Here we summarize the key information from the last AA&MDSIF Scientific Symposium held in Bethesda, Maryland on March 2010. The first part focused on epidemiology, genetics, and pathophysiology of AA, PNH and MDS while the second part was dedicated on treatment of these diseases.

2. Genetics/immunobiology of AA, PNH and MDS

2.1. Genetics and epidemiology

Dr. Pamela Becker from the University of Washington in Seattle introduced and chaired this session dedicated to genetics and epidemiology. The traditional view of clonal evolution in hematopoietic stem cells presumes that leukemogenic events occur in pools of otherwise normal stem cells and are sufficient to sustain the proliferative advantage of the mutant clone. Since MDS clones are defective in both differentiation and maturation, it is unlikely that clonal dysplastic stem cells can have a growth advantage over normal hematopoietic stem cells. Dr. Grover Bagby from the Oregon Health and Science University discussed the key role of the congenital or acquired dysfunction of hematopoietic stem cell pool in the clonal evolution of BMF and in the pathophysiology of de novo MDS. Recent observations clearly suggest that leukemogenic mutations may be functionally neutral in the absence of a selective pressure, such as an environmental event that suppresses the replication or survival of normal stem cells allowing the mutated ones to achieve an advantage. Studies on Fanconi Anemia, a bone marrow failure syndrome that predisposes to clonal evolution, suggest that environmental factors induce global injury in the hematopoietic stem cell pool and result in marrow

* Corresponding author. Tel.: +33 1 42 49 96 60; fax: +33 1 42 49 96 36.
E-mail address: regis.peffaultdelatour@sls.aphp.fr (R.P. de Latour).
[1] All authors equally contributed to the work.

0145-2126/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.leukres.2010.10.010

failure, while also favoring the emergence of MDS clones resistant to the mechanism of injury [1]. Dr. Sharon Savage from the National Institutes of Health (NIH) National Cancer Institute focused on dyskeratosis congenita (DC), a further model of inherited bone marrow failure characterized by an increased risk of cancer. Dr. Savage reported the results from a prospective cohort study of cancer incidence from the National Cancer Institute showing that in patients with DC, the observed to expected number of any cancer was 11-fold higher than in the general population, while the ratio was 2663 for MDS and 188 for acute myeloid leukemia (AML).

Epidemiological studies are crucial in order to identify the environmental risk factors for acquired PMBF. Dr. Mikkael Sekeres from the Cleveland Clinic reported the data of the Surveillance, Epidemiology, and End Results program on MDS of the National Cancer Institute and the Centers for Disease Control and Prevention and of the North American Association of Cancer Registries, as well as the results of six cross-sectional surveys among US hematology and medical oncology specialists. These sources reported an age-adjusted incidence of MDS in the United States of 3.4 cases/100,000 person/year, resulting in over 10.000 new diagnoses annually. However, this figure is probably underestimated, translating in a prevalence of approximately 60,000 patients or more in the U.S. In the same session, Dr. Sara Strom from the M.D. Anderson Cancer Center focused on the most common risk factors for developing MDS, which include advanced age, male gender, exposure to chemo-radiotherapy, smoking, and occupational chemicals such as solvents and agrochemicals.

2.2. Immunobiology

Different groups have already documented the presence of clonal T cells in AA patients, which are specific (or cross-reactive) for autologous hematopoietic stem cells, leading *in vitro* and possibly *in vivo* to an extensive damage of hematopoiesis through both cell–cell interactions and secretion of inhibitory cytokines (IFN-γ and TNF-α)[2]. Dr. P.K. Burnette from the H. Lee Moffitt Cancer Center discussed the dysregulated T cell homeostasis in AA but also in MDS. Dr. Burnette focused on the peripheral homeostasis of self- and non-self-reactive circulating lymphocytes, and on the phenotypic and functional changes of T cells derived through different rounds of antigen-driven activation and proliferation. She showed how a flow cytometry-based study of T cell subsets with specific functional phenotypes may be a surrogate marker for a deranged immune response, as occurring in AA and other bone marrow failure syndromes, such as MDS. Dr. Rodrigo Calado from the NIH National Heart, Lung and Blood Institute discussed telomeres dysfunction. He showed how telomerase complex mutations cause reduction in telomerase activity and telomere shortening, and are associated with several human diseases such as dyskeratosis congenita (DKC1, TERC, TERT, TINF2, NHP2, NOP10), acquired AA (TERT, TERC), familial idiopathic pulmonary fibrosis or cirrhosis (TERT, TERC) and malignancies (TERT, TERC). In AA, short telomeres were also associated with clinical adverse outcome and genomic instability. Dr. Elaine Sloand of the NIH National Heart, Lung and Blood Institute presented MDS as a potential model for immunologically mediated marrow destruction illustrated by the amplification of Vβ subfamily of CD8 cells, the inhibition by CD8 T cells of CFU-GM and CFU-E growth as well as evidence of cytokines dysregulation (TNFα). The second part of her talk was dedicated to immunosuppressive treatment in MDS with significant improvement in the pancytopenia of a substantial proportion of younger individuals with lower-risk disease associated with improved overall and progression-free survival. In the same session, Dr. Antonio Risitano from the University of Naples addressed the question of residual hemolysis for PNH patients treated by Eculizumab. He showed that membrane-bound C3 fragments accumulate *in vivo* on PNH RBCs in patients receiving this treatment because of the persistent low-level spontaneous complement alternative pathway activation (the so-called C3 tick-over). C3-bound RBCs are protected from intravascular lysis by the anti-C5 therapy but become susceptible to entrapment in the reticuloendothelial cells, explaining the residual extra vascular hemolysis [3]. Dr. Risitano also discussed possible novel strategies to overcome C3-mediated extravascular hemolysis: an anti-C3 monoclonal antibody and its de-immunized derivative H17 as well as a fusion protein named TT30, which combines the functional domain of fH with the C3-recognizing domain of the high affinity complement receptor 2.

3. Pathophysiology/molecular targets in MDS

Genomic damage in MDS involves chromosomal abnormalities, mutational events and epigenetic changes. Recently, whole genome scanning technologies have been used to identify novel recurrent defects. Dr. Timothy Graubert from the Washington University in St. Louis discussed the application of the complete DNA sequence of the cancer genome, which recently identified new recurring mutations in IDH1/2 genes in AML [4]. Dr. Jaroslaw Maciejewski from Cleveland Clinic showed the results of high resolution SNP-array studies, which in the last few years led to the identification of several new genetic lesions in MDS and myelodysplastic/myeloproliferative neoplasms (MDS/MPN), including TET2, JAK2, ASXL1, CBL and others. Mutations in genes involved in epigenetic regulation (e.g. TET2 and ASXL1) indicate that epigenetic instability phenotype in malignant cells may be clonally acquired through a specific set of mutations.

Dr. Benjamin Ebert from Harvard Medical School reported the studies from his and other groups, which demonstrate that the MDS associated with 5q deletion likely derives from haploinsufficiency (a dosage effect resulting from the loss of a single allele) of genes mapping to chromosome 5q31–5q33. In fact, partial loss of function of RPS14 phenocopies the erythropoietic phenotype of the 5q- syndrome in normal hematopoietic progenitor cells, while the forced expression of RPS14 rescues the disease phenotype in bone marrow cells from patients with 5q-syndrome, suggesting that defective erythropoiesis in the 5q-syndrome is caused by a defect in ribosomal protein function. The aberrant ribosome biogenesis may cause over-expression and activation of TP53 that result in increased apoptosis of hematopoietic precursors. Deletion of chromosome 5q correlates with loss of two miRNAs that are abundant in hematopoietic stem/progenitor cells, miR-145 and miR-146a. Knockdown of miR-145 and miR-146a in mouse hematopoietic stem/progenitor cells result in thrombocytosis, mild neutropenia and megakaryocytic dysplasia, phenocopying several clinical features of 5q-syndrome [5].

While these achievements shed light on the pathophysiology of ineffective hematopoiesis, it remains poorly understood how dysplastic hematopoietic stem progenitors gain an advantage over the normal stem cells. Dr. H. Joachim Deeg from the Fred Hutchinson Cancer Research Center focused on the dysregulated interaction between stromal and hematopoietic cells in MDS. These defects involve cytokines, adhesion molecules and signalling pathways and sustain abnormal apoptotic patterns in low and high risk MDS. Dr. Stephen Nimer from the Memorial Sloan-Kettering Cancer Center presented the available animal models for MDS, including EVI-1, NPM +/−, SALL4B, NUP98-HoxD13, mutant RUNX1 (AML1), 5q-mice. These models will be crucial to understand how the molecular defects affect self-renewal, proliferation, niche-dwelling, quiescence of MDS hematopoietic stem cells, and will be helpful to identify possible molecular targets for novel therapeutic approaches in MDS.