Peripheral hematopoietic progenitor cell mobilization for autologous transplantation in hematologic malignancies

José Francisco Comenalli Marques Jr.

In this issue of the Revista Brasileira de Hematologia e Hemoterapia, Gabús et al.(1) are publishing an interesting article about hematopoietic progenitor cell mobilization for autologous transplantation in hematologic malignancies. Although the analysis was retrospective, they utilized the abundant statistical tools and compared two successive groups of patients with similar numbers and over similar periods, in order to compare patients in respect to the origin of the growth factor used, different brands in the first group and a specific growth factor (JP Filgen - Clausen filgrastim) in the second.

First, it is worth noting some features of the profile of the service in which the mobilization was analyzed that performs a large number of autologous compared to allogeneic transplants (80% and 20% respectively) and a slight predominance of patients from the Uruguayan National Health System. The target collection of CD34+ cells was consistent with the literature.

Some results should be mentioned and discussed:
1. The mobilizations were very effective with collections of the desired numbers of CD34+ cells using few leukapheresis procedures from most patients;
2. The 10% mobilization failure rate corroborates medical literature, both for the overall proportion, in respect to age and autologous transplantation and active disease. However, many patients with multiple myeloma had bad mobilizations even though characteristically these patients mobilize well, better than those with Hodgkin's lymphoma, for example. One possible explanation for this may be related to the chemotherapy used, melphalan, which used to be considered a single line chemotherapy before, but with significant negative impact on mobilization, much more than a number of other chemotherapy lines;
3. The strategy to try to collect from "bad mobilizers" in this series was very effective whether by repeating the mobilization (majority) or collecting cells directly from bone marrow;
4. Another important feature to be commented on is the relative small proportion of patients mobilized with filgrastim associated with chemotherapy (14.6%) as most were mobilized with growth factor alone (85.4%). As the paper states, the use of chemotherapy in combination with filgrastim is reserved for patients when difficulty in obtaining CD34+ cells is expected or when there is any additional benefit from chemotherapy, such as to better control the underlying disease. We believe that in vivo "purging" before mobilization will help patients to enter the autologous transplantation procedure closer to remission, even considering the higher cost (more growth factors, hospital, antibiotics, transfusions, etc) and the greater difficulty to obtain CD34+ cells. But this is still an open question in the medical literature;
5. A very important point to discuss is that Group B, i.e., those mobilized with Filgen JP (Clausen filgrastim) used a significantly lower amount of filgrastim but the quality of mobilization was similar, which may be more efficient in relation to the filgrastim used previously (Group A).

Our group has been studying for several years, strategies to optimize the collection of hematopoietic progenitor cells from peripheral blood by apheresis, considering various parameters. Our first work was published in 2000,(2) when we had observed that shorter periods between chemotherapy, mobilization and recovery of total leukocytes, improve the collection in terms of fewer leukaphereses needed to obtain CD34+ cells. The parameter to begin apheresis was recovery after the nadir leukocyte count reached 1000 cells/mm³. Following that, in a study published in 2006,(3) we analyzed other parameters to predict the ideal time to start apheresis, in order to reduce the number of procedures. At that time, we began to use the same guideline that Gabús et al.(1) i.e., when the CD34+ count in peripheral blood reached 10 cells/mm³. We were able to demonstrate, through sequential daily blood cell and CD34+ counts, that the best day can be predicted by a formula that considers hemoglobin on the day of mobilization chemotherapy and the number of days between chemotherapy mobilization and when the CD34+ cell count in peripheral blood reached
10 cells/mm³. Thus, we discovered that we were collecting too early.

Using this formula prospectively, we analyzed in terms of "cohort", this new strategy of mobilization and observed that this formula was useful in patients with lymphoma, but not with multiple myeloma.

As we can see with these considerations above, this is an important issue that deserves to be further studied and published, thus supporting the initiative that Gabús et al. had in publishing this article.

References
and those with either +8 or 12p- abnormalities was observed. A prospective FISH study of 107 MF patients correlated cytogenetic findings with clinical outcome and survival. Interestingly, FISH was superior to karyotyping in eight karyotype-normal patients, who presented various chromosomal abnormalities. The main recurrent chromosomal aberrations did not correlate with clinical features or prognosis. In contrast, patients with the 7q- or -7 chromosomal abnormalities had worse outcomes.

The number of cytogenetically studied untreated ET patients is limited. Cytogenetic abnormalities occur in less than 55% of patients at diagnosis and are non-specific and are therefore of limited value. (3)

At the molecular level, there are no specific biologic markers for MPNs, however, there are some that provide additional tools in establishing diagnosis, especially for PV.

**JAK2 V617F** is the most prevalent mutation in BCR-ABL1-negative MPN with mutation frequencies of 96% in PV, 55% in ET and 65% in MF. The presence of the **JAK2 V617F** mutation in MPN has been associated with older age, higher hemoglobin count, leukocytosis and lower platelet count. In PV, a higher mutant allele burden has been associated with pruritus and fibrotic transformation, but does appear to affect the risk of thrombosis, survival or leukemic transformation in PV and ET. The **JAK2 V617F** mutation is sufficiently prevalent in MPNs to be useful as a clonal marker, with screening of this mutation being indicated for the evaluation of erythrocytosis, thrombocytosis, splanchic vein thrombosis and otherwise unexplained BCR-ABL1-negative granulocytosis. However, the mutation does not provide additional value in the presence of unequivocal morphologic diagnosis and its presence does not necessarily distinguish one MPN from another or provide useful prognostic information. **JAK2** exon 12 mutations are relatively specific to **JAK2 V617F**-negative PV and are diagnostically useful. Screening of these mutations is indicated only in the presence of **JAK2 V617F**-negative erythrocytosis which is associated with a subnormal serum erythropoietin level. (4)

Reduced expression of the thrombopoietin-receptor, c-Mpl, was the first molecular marker described in PV. Moliter et al. reported a reduced expression of the c-Mpl in PV, as well as in MF, but not in patients with ET. However, subsequently, several other studies have shown conflicting results. Thus, reduced c-Mpl expression has been reported in ET patients, but at different rates. **MPL** mutations are neither frequent nor specific enough to warrant their routine use for MPN diagnosis, but they may be useful in resolving specific diagnostic problems. To date it is unclear whether this molecular change could contribute to the molecular pathology of MPNs. (5)

**MPL** and **JAK2 V617F** mutation analysis was performed in 603 patients with primary myelofibrosis (PMF) seen at the Mayo Clinic, USA (n = 329) or the University of Florence, Italy (n = 274). **MPL** mutations were detected in 49 (8.1%) patients and **JAK2 V617F** in 350 (58%); four patients showed both mutations. Patients without these mutations were significantly younger in both patient cohorts (p-value < 0.01). In the Florence cohort, the presence of the **MPL** mutation was associated with older age (p-value < 0.01) and constitutional symptoms (p-value = 0.04) and **JAK2 V617F** with higher hemoglobin (p-value < 0.01) and leukocyte counts (p-value = 0.03). Neither patient cohort showed significant associations with platelet count, hemoglobin < 10g/dL, abnormal/unfavorable karyotype, spleen size or prognostic score distribution. At the time of this publication, 240 deaths and 79 leukemic transformations were documented among all 603 study patients. Multivariable analysis showed no significant difference in overall or leukemia-free survival between the three molecular subgroups. The study concluded that the presence of the **MPL** mutation has a narrow, inconsistent phenotypic effect in PMF and does not influence overall or leukemia-free survival.

In conclusion, in MPNs, the chromosomal gains and deletions are the prominent cytogenetic findings. Cytogenetic analysis has an important role in establishing the diagnosis and disease outcome. Although the discovery of alterations of certain genes such as **JAK2** has not translated into changes in the treatment of the PV, ET and MF, it represents the most important advance in understanding the pathogenesis, contributing to a more accurate classification and management of patients. (6)

References


Secondary myeloid neoplasias: an emerging group of diseases

Secondary myeloid neoplasias are a heterogeneous group of diseases characterized by the proliferation of myeloid cells; they were recently recognized by the World Health Organization (WHO) as an entity. The wide use of chemotherapy and better diagnosis of hematological malignancies has caused a growth in the number of secondary malignancies. Most of them are myeloid: a) myelodysplastic syndromes (MDS), a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis and dysplastic changes in bone marrow and peripheral blood with the risk of transformation to acute myeloid leukemia (AML) or b) sometimes the previous disease directly evolves to an overt AML. Usually the prognosis of patients with a secondary myeloid neoplasia is poor, especially when the previous disease is a MDS. However, patients may achieve a complete response. In this situation, progenitor stem cell transplantation is the best therapy.

Cytogenetic analysis still plays a pivotal role in the diagnosis of hematological diseases. Cytogenetics and mutational analysis are the main prognostic tools in both AML and MDS. For this reason, cytogenetic studies are critical in the correct management of these diseases. There are several cytogenetic abnormalities associated with better prognosis, such as translocations involving core binding factors in AML patients, and losses in 20q, 5q or chromosome Y in MDS. In contrast, many others abnormalities are associated with dismal prognoses, such as the presence of a complex karyotype, abnormalities of either chromosome 3 or chromosome 7 and, in case of AML, the loss of the long arm of chromosome 5.

All of these abnormalities are included in the new staging system for MDS (IPSS-2). Recently new data regarding the presence of abnormalities in chromosome 7 in primary MDS showed that the presence of a partial deletion of the long arm of this chromosome (7q-) is associated with a better prognosis than monosomy 7. This abnormality is a common event in secondary MDS and AML and the potential value of this observation in secondary MDS should be addressed. In this issue of the Revista Brasileira de Hematologia e Hemoterapia a new observation highlighted the importance of performing cytogenetic studies in secondary MDS. Over recent years, the wide use of microarrays and, more recently, the possibility of sequencing the human genome have provided new insights into knowledge of the molecular mechanisms involved in MDS and AML. Analysis of the gene expression profile by means of microarray technology demonstrated the presence of new pathways involved in the pathogenesis of these disorders, although studies focusing on secondary myeloid diseases are lacking. Since the sequencing of the entire genome of the first hematological malignancy, a patient with AML, several papers have shown the interest of the detection of new genes involved in these diseases. Some of these papers have also described the involvement of new functions involved in myeloid diseases such as the spliceosome mechanism that could play an essential role in the genesis of both MDS and AML. Therefore, near future investigations should provide more information of the genes involved in secondary myeloid diseases. The challenges will be to understand these genes which are thought to be drivers in the genesis of secondary myeloid neoplasias and, more importantly, to identify new therapeutic targets.

References

On the relevance of outpatient intravenous iron therapy for anemia management

Iron is an essential micronutrient, as it is required for an adequate erythropoietic function, oxidative metabolism and cellular immune response. In the human body, iron metabolism pathways include absorption from food, distribution to target cells, storage and recycling. Dietary iron is found as heme (10%) and non-heme (ionic, 90%) forms; absorption occurs at the apical surface of duodenal enterocytes via different, tightly regulated, mechanisms with absorption balancing losses (1-2 mg/day) as no active iron excretory mechanisms exist. Dietary non-heme iron primarily exists in an oxidized (Fe³⁺) form that is not bioavailable and must first be reduced to the Fe²⁺ form by a ferrireductase enzyme, that uses vitamin C as a coenzyme, before being transported across the intestinal epithelium by the divalent metal transporter 1 (DMT1). Heme iron is transported into the enterocyte by a putative heme carrier protein 1 and metabolized by heme oxygenase to release Fe²⁺, which enters a common pathway with dietary non-heme iron before it leaves the enterocyte. Iron is exported by ferroportin 1 (the only putative iron exporter) across the basolateral membrane of the enterocyte into the circulation (absorbed iron) where it binds to transferrin and is transported to sites of use and storage. Transferrin-bound iron enters target cells – mainly erythroid cells, but also immune, muscle and liver cells – through a process of receptor-mediated endocytosis.

Erythrocytes contain up to 65-70% of body iron. Senescent erythrocytes undergo phagocytosis by macrophages of the reticuloendothelial system, heme is metabolized by heme-oxygenase and the released iron stored as ferritin. Iron will later be exported from macrophages to transferrin, a process accomplished primarily by ferroportin 1, the same iron-export protein expressed in the duodenal enterocyte and in ceruloplasmin. The amount of iron required for a daily production of 300 billion red blood cells (20-30 mg) is provided mostly by macrophage iron recycling. Thus, this internal turnover of iron is essential to meet the requirements of erythropoiesis.

Hepcidin, synthesized by hepatocytes in response to low iron levels, inflammation, hypoxia and erythropoiesis, is the main iron homeostasis regulatory hormone. Hepcidin binds ferroportin on enterocytes, macrophages and hepatocytes triggering its internalization and lysosomal degradation. Therefore, increased hepcidin secretion may lead to iron deficiency (ID) and anemia. As stated above, under physiological conditions, there is a balance between iron absorption and iron losses in the human body. Thus, ID and iron deficiency anemia (IDA) may result from the interplay of three distinct risk factors: increased iron requirements, limited external supply and increased blood loss. ID can be either absolute or functional. In absolute ID, iron stores are depleted; in functional ID (FID), iron stores, although replete, cannot be mobilized as fast as necessary from the macrophages of the reticuloendothelial system to the bone marrow (treatment with erythropoiesis stimulating agents and inflammation are the most common causes of FID). In chronic inflammation, the excess of hepcidin decreases iron absorption and prevents iron recycling, resulting in hypoferraemia and iron restricted erythropoiesis, in despite of normal iron stores, and finally anemia of chronic disease (ACD), which can further evolve to ACD plus true ID (ACD + ID).

Investigation of ID in the clinical practice mostly relies on laboratory tests which fall...
into two categories: measurements providing evidence of iron depletion in the body and measurements reflecting iron deficient red cell production. The appropriate combination of laboratory tests, together with clinical signs and symptoms, will help to establish a correct diagnosis of anemia and ID status. In the absence of inflammation (e.g., serum concentrations of C-reactive protein < 0.5 mg/dL), true ID can be defined by a ferritin level < 15-30 ng/mL. In the presence of inflammation, true ID could be defined by a ferritin concentration < 100 ng/mL and a transferrin saturation (TSAT) < 20%, whereas FID is generally defined by a ferritin concentration > 100 ng/mL and a TSAT < 20%. Patients should be considered to suffer from IDA when they present with low Hb (men < 13 g/dL, women < 12 g/dL), TSAT < 20% and ferritin < 30 ng/mL, but no signs of inflammation (mean corpuscular hemoglobin rather than mean corpuscular volume became this is the most important red cell marker for detecting ID in circulating red blood cells).

Patients should be considered to suffer from ACD, also called anemia of inflammation, when they have: anemia, evidence of chronic inflammation, and TSAT < 20%, but normal or increased serum ferritin concentration (> 100 ng/mL). ACD, as well as FID, is frequent among patients with inflammatory disease without apparent blood losses (e.g., rheumatoid arthritis, renal failure or chronic hepatitis). ACD may evolve to ACD + ID which is characterized by low transferrin saturation (TSAT < 20%), and low serum ferritin concentrations. This type of anemia is more frequent in patients with inflammatory diseases and chronic blood losses (e.g. inflammatory bowel disease, hemodialysis).

For intermediate serum ferritin concentration (30-100 ng/mL), a serum transferrin receptor (sTfR)/log ferritin ratio < 1 indicates FID and sTfR/log ferritin ratio > 2 indicates true ID. In addition, there are several important hematologic indices that may also help in the diagnosis of ID in ACD (e.g., reticulocyte Hb content [CHR] or hypochromic red blood cells [HYPO]), but unfortunately they are only available in specific hematology analyzers.

Oral iron supplementation is adequate for treating ID in most clinical conditions. In the absence of inflammation or significant ongoing blood loss, the administration of oral iron can correct anemia, provided significant doses can be tolerated. However, although conventional wisdom "says" that up to 200 mg of elemental iron per day is required to correct IDA, this is incorrect and lower doses (50-100 mg) can also be efficacious.

Intravenous (IV) iron supplementation is another treatment option for ID (intramuscular administration is no longer recommended). Seven different products are principally used in clinical practice: iron gluconate, iron sucrose, high-molecular-weight iron dextran (HMWID), low-molecular-weight iron dextran (LMWID), ferric carboxymaltose, iron isomaltoside 1000 and ferumoxytol. Their efficacy to treat anemia is directly related to the amount of iron administered, although differences in core size and carbohydrate chemistry determine pharmacological and biological differences between the different iron complexes. This efficacy has been consistently proved in a variety of clinical settings, including nephrology, oncology, cardiology, digestive tract diseases, obstetrics and gynecology, rheumatology, and more recently surgery. With such evidence available, one would think that IV iron would be widely used in these clinical settings. Yet, with the exception of chronic kidney disease, it can be estimated that treatment with IV iron is considered in less than 5% of patients who would clearly benefit from receiving it. The reason for this resistance to use IV iron may be that there exists a generalized fear of anaphylactic reactions and deaths based on reports of poorly characterized, infrequent reactions, when in fact the overwhelming majority of serious events occur when HMWID is used. Therefore, with the exception of HMWID (increased rates of severe side effects and deaths), the acute safety differences among the IV iron products are small and clinically irrelevant when given at the recommended doses (and, more importantly, smaller than those associated with red cell transfusions), though comparator trials are needed to be certain.

Usually, intravenous (IV) iron was indicated in situations such as intolerance, contraindication or inadequate response to oral iron (e.g., inflammation, erythropoiesis stimulating agent administration). The study by Cançado et al. published in this issue of Revista Brasileira de Hematologia e Hemoterapia clearly exemplifies these indications for IV iron replacement. They evaluated the efficacy and safety of IV iron sucrose (IS, 200 mg/week, until anemia correction or replenishment of calculated ID; 515 infusions) for the treatment of 86 adult patients with IDA, intolerance or no effect of oral iron therapy. IS administration led to an average increase of hemoglobin levels of 3.5 g/dL (≥ 2 g/dL in 86% of patients) and an anemia correction rate of 67%, while ferritin levels increased by 87 ng/mL and no moderate or serious adverse drug reactions were witnessed. These data add to the concept that modern IV iron formulations are a safe and effective alternative for anemia management, as they present several advantages over oral supplementation. The administration of IV iron allows up to a five-fold erythropoietic response to significant blood-loss anemia in normal individuals, hemoglobin starts rising in a few days, the percentage of responding patients is higher and iron stores are increased. In addition, as oral iron therapy is time-consuming, these data should also drive a broader use of IV iron supplementation in other clinical scenarios, such as in anemic patients presenting with short time to surgery, especially in those with severe anemia, significant ongoing bleeding and/or high perioperative blood loss.

In this regard, the efficacy of intravenous IS administration (1000 ± 400 mg/patient over 3-5 weeks) for correction of preoperative anemia in 84 patients who were scheduled for major elective surgery (30 colon cancer resections, 33 abdominal hysterectomies, 21 lower limb arthroplasties) has been recently evaluated. Administration of IV iron caused a significant increase of hemoglobin levels (2.0 ± 1.6 g/dL) and anemia was resolved in 59% of patients. No life-threatening adverse effect was witnessed, and overall transfusion rate was only 24%. However, the main disadvantage of IS was the need for multiple infusions...
Allergic rhinitis and association with the O blood group

Clara Carpeggiani

Institute of Clinical Physiology, National Research Council – CNR, Pisa, Italy

Affecting about 600 million people worldwide, allergic rhinitis (AR) is an atopic disease that has a significant impact on the quality of life. The prevalence has increased abruptly in recent years in most Western countries. The disease, also known as hay fever or polinosis, occurs in individuals with a sensitized immune system. The allergen triggers the production of IgE antibodies, which bind to mast cells and basophiles containing inflammatory mediators such as histamine, which are then released into the bloodstream.

This is a complex multifactorial allergic disease with environmental and genetic components. One hypothesis to explain the steep rise in allergic diseases in recent years is the ‘hygiene hypothesis’: the excessive ‘cleanliness’ of the environment has led to a decline in the infectious stimuli that are necessary in the development of the immune system. Many other factors have been suggested to play a role in the development and expression of atopic diseases including changes in lifestyle, pollution, dietary changes with diminished nutritive value and stress. The strongest risk factors in the development of allergic symptoms are a family history of allergies, secondhand cigarette smoke exposure and male gender.

The mechanism of inheritance is still unclear. Familial aggregation has been described for many years. It is commonly believed that allergies are caused by multiple interacting genes, some having a protective effect and others contributing to the disease pathogenesis with each gene being influenced by the environment in a different way. Twin studies have provided key evidence for a genetic effect as there was a greater concordance of allergic manifestations observed in monozygotic compared to dizygotic twins; the heritability for atopy is estimated to range between 50 and 84% of these twins. Many candidate genes have been suggested in atopy and allergic diseases. The most important linkages include the genes for IL-4, IL-13, HLA-DRB, TNF, LTA, FCER1B, IL-4RA, ADAM33, TCR α/δ, PHF11, GPRA, TIM, p40, CD14, DPP10, T-bet, GATA-3, and...
FOXP3. However, no genome wide association study has been performed specifically for allergic rhinitis.

ABO is the major human blood group system, the distribution of which varies between countries. ABO blood groups are genetically transmitted through locus 9q34 of chromosome 9. The ABO, H, and Lewis histo-blood group antigens are determined by the action of glycosyltransferases that attach sugar molecules to disaccharide precursors on the red blood cells. The addition of fucose to these disaccharide precursors creates the H antigen and further modifications to the H antigen by glycosyltransferases leads to the synthesis of the blood group antigens encoded by the ABO gene. The O allele does not produce an active enzyme and has α-fucose (1 → 2) galactose disaccharides [O(H) structures] on its cell surface while in type A or B individuals, the O antigen is capped by the addition of α-N-acetylgalactosamine or α-galactose residues, respectively. The A and B genes differ in a few single-base substitutions that change four amino-acid residues which may cause differences in A and B transferase specificity. A critical single-base deletion was found in the O gene, which results in an entirely different, inactive protein incapable of modifying the H antigen.

The Lewis blood group is a minor blood group that is related to saliva secretor status. Saliva ABH secretor determination is based on testing for blood group antibodies in saliva. ABH secretors are identified by the secretion of ABO antigens in fluids such as saliva, sweat, tears and breast milk. Almost 15% of people are ABH non-secretors. The secretor gene that encodes for 2-alpha-L-fucosyltransferase (FUT2) is inherited in codominant fashion and has a normal and an inactive form. The O allele does not produce an active enzyme and has α-fucose (1 → 2) galactose disaccharides [O(H) structures] on its cell surface while in type A or B individuals, the O antigen is capped by the addition of α-N-acetylgalactosamine or α-galactose residues, respectively. The A and B genes differ in a few single-base substitutions that change four amino-acid residues which may cause differences in A and B transferase specificity. A critical single-base deletion was found in the O gene, which results in an entirely different, inactive protein incapable of modifying the H antigen.

Studies evaluating the relationship between ABO blood group status and atopic diseases have appeared in the literature since the late sixties. Apparent discordant results have been reported. In 1964, the observation that ABO agglutinins are present in a wide variety of pollens from grasses, flowers and trees, raised the possibility that these agglutinins might interact with cells containing blood group antigens in the respiratory epithelium, an effect that would neutralize in secretor patients. In 1968, Denborough was the first to study secretor status in allergic diseases of the respiratory tract comparing 435 subjects with hay fever and asthma and 411 controls. No significant differences in ABO blood group distribution, secretor status and salivary isoglutinins were detected between patients and controls. Blood group A and/or B antigens and atopic conditions such as rhinitis, hay fever and asthma, and the shift appeared to be largely due to a contribution from female patients with pollinosis. The majority of the studies reported an association between atopic diseases such as rhinitis and the O group, while resistance was associated to A phenotypes. In particular, a higher susceptibility was found for the O group in Lewis-negative or non-secretor children and adults. The results of the paper by Falsarella et al. published in this edition of the Revista Brasileira de Hematologia e Hemoterapia are in agreement with previous conclusions and underlines the male gender impact on the association.

Glycosyltransferases are controlled by the ABO system to build oligosaccharide structures on the cell surface of erythrocytes and vascular endothelium, as well as in the exocrine secretion systems of the respiratory tract. Alpha-2-fucosyltransferases FUT1 (H) of red blood cells and vascular endothelium, and FUT2 (Secretor positive) of the exocrine secretion system, are structural genes that collaborate with glycosyltransferases. Studies based on separate analysis of the ABO and Secretor systems have led to discordant results, probably because of the complexity of the interactions between these genes. When a combined analysis of ABO blood groups and secretor phenotypes was performed, a cooperative interaction between the two systems was described. Blood group O/non-secretor subjects had lower lung function values and higher prevalence of atopy. The product of ABO and secretor genes seems also to influence the adhesion of infectious agents, thus having a modulator effect on viral and bacterial respiratory tract infection. Since the oligosaccharide composition of the cell membrane and mucosal secretions change with age and influence the adhesion of infectious agents, the age pattern of atopic diseases could reflect the interaction between cell maturation and oligosaccharide structure and its effect on susceptibility to viral and bacterial agents.

The limited number of patients enrolled in the studies is the biggest limitation of the literature on this issue. More studies with large populations could be helpful to determine the exact function of the involved genes and the gene-environment interaction which could help to better understand the pathology, prevention and treatment of this disease.

References
Clinical guidelines in Hematology

Wanderley Marques Bernardo

Medicine School, Universidade de Sao Paulo – USP, Sao Paulo, SP
Centro Universitário Lusíada – UNILUS, Santos, SP, Brazil

Clinical guidelines are now a powerful tool in decision making in the complex process of healthcare. There is no absolute definition of its impact on the clinical outcomes and in different patient populations. Nevertheless, its role is unquestionable in the regulation and organization of the healthcare system as a whole. (1-8)

Evidence-based clinical guidelines balance the diverse interests involved during the process to ensure that patients receive an adequate standard of healthcare. Through clinical guidelines we can compare our experience with recommendations, which not only teaches us and brings our knowledge up-to-date, but also allows us to reflect on the main issue: what level of uncertainty am I accepting with my current conduct of this patient? (9-15)

The central principle of the Associação Médica Brasileira (AMB)/Conselho Federal de Medicina (CFM) Guidelines Program is to prepare the physician to answer four basic questions: a) what do I do in my clinical practice; b) for whom do I do it; c) how do I do it and d) why do I do it? (16)

The development of recommendations can be interpreted as a way to limit medical autonomy, but in fact, it is to make our actions in healthcare in Brazil transparent, clearly stating the strength of scientific evidence that supports each of these conducts by estimating the level of uncertainty involved in decision making. (17-22)

We established standards, providing conduct options focused on the patient in relation to what we do: recommendations for diagnosis, prevention, treatment and prognosis; for whom we do it: patients with indications to meet their expectations and individuality, and never forgetting the minorities; how we do it: defining the method by which to develop our detailed and explicit conduct; and why we do it: to support our decisions on the benefits, risks and harm to patients. (23-26)

The AMB-CFM Guidelines Program together with the societies of medical specialties, members of the AMB, has already prepared 500 clinical guidelines and today has about 120 in development. In addition, continuing medical education and participation in international networks that develop evidence-based guidelines is included in the Guidelines Programs.

In 2011, Brazilian hematology through its society (the Associação Brasileira de Hematologia e Hemoterapia – ABHH) started an unprecedented process of developing evidence-based protocols within the AMB-CFM Guidelines Program. The association initially chose six major hematological diseases: Sickle cell anemia, chronic myeloid leukemia, acute promyelocytic leukemia, non-promyelocytic leukemia, idiopathic thrombocytopenic purpura and multiple myeloma.

Each theme (Guideline) is composed of important clinical questions (on average 15) prepared by experts. These questions are structured using the acronym, PICO (P: patient, I: Intervention: C: Comparison, O: Outcome) as a guide to search available evidence by an extensive systematic review of the literature to find evidence to support the recommendations for each clinical question. The recommendations are based on the strongest scientific evidence and aim to help hematologists make their decisions on each individual patient. (3,16,19,21)

In mid-2012, the first six issues will be completed initiating a series of feasible guidelines developed using a rigorous methodology written in a clear and objective language. Without doubt, participants at all levels of the healthcare system will benefit, but mostly these benefits will be reflected in the care provided to hematology patients in Brazil.

We recognize the difficulties of obtaining and critically analyzing the evidence, the pressure of interest that are not always directed to the care of patients and the difficulties of the National Health System in relation to its structure, diversity and inequality. But we also know the effort and determination of many, who, through the guidelines, will establish a discerning, flexible, ethical, and reflective language, based on evidence that meets the basic needs and expectations of patients. (2,21,22)
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