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SP 07

Bone marrow failure

Rodrigo T. Calado

Aplastic anemia may be the result of the immune attack against hematopoietic stem and progenitor cells or the impairment of appropriate hematopoietic stem cell function due to inherited genetic defects. Although bone marrow transplantation is the preferential therapy for severe cases, the majority of patients lack a suitable sibling donor. The thrombopoietin receptor agonist eltrombopag has been recently added to immunosuppressive therapy, reaching high response rates and overall survival, rivaling matched-donor transplant results. Additionally, genetic defects in telomere-maintenance genes appear to be the most prevalence etiology of inherited aplastic anemia. Sex hormones may recover hematopoiesis in these cases. The occurrence of somatic genetic mutations in immune and inherited aplastic anemia may help to understand the complex dynamics of hematopoietic stem cells in vivo.

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SP 08

Immunocompromised patients: prevention, diagnosis and therapy of infection

Marcio Nucci

Patients with bone marrow failure are at increased risk to develop severe infection. The main immunodeficiency is neutropenia, particularly in patients with acute leukemia and severe aplastic anemia. In addition, treatment-related immunodefficiencies further increase the risk of infection, including mucositis caused by intensive chemotherapy, and T-cell immunodeficiency that follows immunosuppressive therapies for aplastic anemia. In neutropenic patients, prophylactic strategies focus on the prevention of bacterial and fungal infections. A key element in the management is the prompt initiation of empiric antibiotic therapy in febrile neutropenic patients, focusing on Gram-negative bacteria. With this regard, the emergence infection caused by multi-drug resistant Gram-negative bacteria is a major challenge, because inappropriate antibiotic coverage is associated with high mortality rates. Therefore, it is imperative to know local epidemiology in order to select the most appropriate antibiotic regimen. Likewise, changes in the initial empiric antibiotic regimen should be driven by objective parameters and not just fever. For invasive fungal disease, while the empiric antifungal therapy is still used, this strategy has been replaced by a preemptive diagnostic-driven approach. In this strategy, serial (2–3×/week) serum galactomannan and chest tomograpy drive the start of antifungal therapy. Finally, while the wise and appropriate employment of all these strategies is very important, recovery from neutropenia is the main prognostic factor. Therefore, every efforts must be devoted to control the underlying disease.

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SP 09

Paroxysmal nocturnal hemoglobinuria pnh

Hanan Hamed

Objective: PNH is a condition in which uncontrolled complement activity leads to systemic complications, principally through intravascular hemolysis and platelet activation. It arises through a somatic mutation of the phosphatidylinositol glycan A (PIG-A) gene in bone marrow stem cells,[1,2] resulting in disruption to glycosylphosphatidylinositol (GPI) biosynthesis.[3]

Results: Among the deficient proteins are the complement regulatory proteinsCD55 andCD59, resulting in increased complement sensitivity of PNH cells, intravascular hemolysis, promotion of inflammatory mediators, and systemic hemoglobin release.[4] Patients with PNH can present with multisystemic clinical manifestations due to intravascular hemolysis, thrombosis and bone marrow failure.[5] Symptoms are therefore often non-specific, ranging from loss of vision (due to retinal thrombosis), headache and nausea/vomiting (due to cerebral thrombosis), pulmonary hypertension (due to pulmonary embolism), anaemia, through to pain and swelling in the lower extremities (due to deep vein thrombosis), renal failure and other symptoms affecting different systems.[6] Thromboembolism is the most common cause of mortality in patients with PNH and accounts for approximately 40% to 67% of deaths of which the cause is known. Further, 29% to 44% of patients with PNH have been reported to have at least 1 thromboembolic event during the course of their disease, although the reason(s) a thrombotic event may suddenly occur remains an enigma.[7–9] Platelet activation, complement-mediated hemolysis, impaired nitric oxide (NO) bioavailability, impairment of the fibrinolytic system, and inflammatory mediators are all proposed mechanisms and thought to be responsible for the increased thrombotic risk in patients with PNH. Multiple factors are likely to contribute to any one thrombotic event in patients with PNH.[10]

Conclusion: Therapeutic strategies include terminal complement blockade and bone marrow transplantation. Eculizumab, a monoclonal antibody complement inhibitor, is highly effective and the only licensed therapy for PNH.[11] The therapeutic anti-C5 antibody eculizumab (Soliris, Alexion)

has proven effective in controlling intravascular hemolysis in vivo, leading to remarkable clinical benefit in a majority of PNH patients.[12,13] Yet, persistent C3 activation occurring during eculizumab treatment may lead to progressive deposition of C3 fragments on affected erythrocytes and subsequent C3-mediated extravascular hemolysis, possibly limiting the hematologic benefit of anti-C5 treatment.[14,15] Thus, upstream inhibition of the complement cascade seems an appropriate strategy to improve the results of current complement-targeted treatment.[16,17]

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SP 10

Access to cancer medicines and targeted therapies in developing countries

Zeba Aziz

In LMIC national cancer control programs are barely existent. Emphasis is mainly focused on fighting infectious disease, maternal child mortality and now fighting the Covis-19 catastrophe.

Pakistan is a LMIC with allocation of only 2.7% of the GDP to health. We have approximately 173,937 new cancers and a mortality of 118,442. Health expenditures do not correlate with outcomes especially for the marginalized population. Development and implementation of national NCD control programs for screening of common cancers and early detection are either non-existent or sporadic as a result cancers are usually diagnosed late and present challenges to therapy on all fronts especially in the indigent population.

Challenges include poverty, ignorance, lack of access to cancer centers, lack of access to basic cancer therapy and suboptimal treatment. This includes surgery, radiation and cancer therapy including supportive care. Simultaneously there is a dearth of human resource and cancer care providers to diagnose treat and provide supportive care to cancer patients.

Access to new biologics and targeted therapies present a challenge to the already strained health care budget. Current status of cancer care will be discussed in Pakistan.

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SP 11

Ph-positive and ph-like all: how can we further improve?

Robin Foà

While in childhood ALL the cure rates can be over 80%, in adults the prognosis still remains unsatisfactory. Important advancements have however occurred in the management of adult patients based on the biology of the disease. Ph+ ALL is an illuminating example of how the understanding of a specific genetic abnormality has led over time to the use of targeted therapies. The results obtained with tyrosine kinase inhibitors (TKI) used upfront in adult Ph+ ALL have changed our approach to this condition in patients of all ages. It is thus mandatory that the abnormality is rapidly investigated at presentation. In the GIMEMA network, the presence or absence of the BCR-ABL fusion is tested centrally within one week from diagnosis of ALL, during the steroid pre-phase. TKIs – alone or in combination with chemotherapy – have markedly improved the rates of response and overall survival of Ph+ ALL. The Italian cooperative group GIMEMA over the years has been using an induction strategy based on the use of a TKI (1st, 2nd and 3rd generation) plus steroids and CNS prophylaxis, with no systemic chemotherapy. This has led to a hematologic CR in 94–100% of patients (with no upper age limit) with virtually no deaths in induction. A proportion of patients can obtain a molecular response. Some elderly patients treated only with TKIs are alive and well after many years from diagnosis. Other groups have used a combination between a TKI and de-intensified chemotherapy, in order to reduce the toxicities (and deaths) associated with conventional chemotherapy plus a TKI. With the advent of TKIs, the induction of Ph+ ALL patients – if identified promptly – is a solved issue. Since patients who achieve a molecular response fare significantly better, a molecular response should be the primary endpoint of treatment. Allogeneic stem cell transplant has always been considered the only curative strategy for Ph+ ALL patients. New strategies are however under active investigation. In the last GIMEMA LAL 2116 front-line trial an induction-consolidation strategy based on the use of dasatinib followed by at least two cycles of the bispecific monoclonal antibody blinatumumab were used. This chemo-free induction-consolidation approach is associated with very high rates of molecular response (Chiaretti et al, ASH 2019). In childhood Ph+ ALL, the protocols so far still use an induction based on a combination of chemotherapy plus a TKI.

Great attention has been raised by the so-called Ph-like ALL, a subgroup associated with an unfavorable prognosis. Evidence has been provided that this is contributed by the persistence of minimal residual disease following conventional chemotherapy. Attempts are being carried out by incorporating TKIs or other inhibitors. The GIMEMA LAL 2317 has used blinatumomab in the front-line Ph- ALL protocol (recently