dexamethasone plus daratumumab (POLLUX TRIAL),[3] carfilzomib (ASPIRE TRIAL),[4] ixazomib (TOURMALINE TRIAL),[5] or elotuzumab (ELOQUENT TRIAL).[6] In all these trials, results confirmed that triplet regimens were superior in response rate and progression-free survival. If the patient is considered refractory to lenalidomide, a proteasome inhibitör combination is a standard for treatment in early relapse. Carfilzomib plus dexamethasone was compared to bortezomib and dexamethasone in the Endeavor study and demonstrated superiority in progression-free survival (PFS) and overall survival (OS).[7] Carfilzomib + dexamethasone (KD) combination was recently compared as a control arm versus daratumumab plus KD (Candor Trial).[8] In this phase[3] trial, a superiority in PFS was demonstrated for the triple combination. Daratumumab, bortezomib, dexamethasone combination (Castor Trial)[9] and pomalidomide, bortezomib, dexamethasone (OPTIMISMM)[10] are also good options for this subset of patients, previously exposed and refractory to lenalidomide. Both trials demonstrated superiority in response rate and PFS. New clinical trials are addressing innovative strategies, particularly with belantamab mafodotin, an anti-BCMA antibody, and with anti-BCMA – CAR T-cell. Both demonstrated high efficacy in terms of response rate in Phase1/2 Trials, including heavily pretreated and Penta-refractory patients.[11,12] Large phase 3 trials are planned for hopefully incorporate these strategies to MM treatment.

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SP 06

Current therapy for indolent lymphomas

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Introduction: Indolent lymphomas are neoplasms of the mature B-cell that have the survival measure in years even without direct treatment. This group contains follicular lymphoma, lymphoplasmacytic lymphoma and marginal zone lymphoma. Mantle cell lymphoma, although can have an indolent course, it's not included here.

Follicular lymphoma (FL): FL is the second in prevalence between non-Hodgkin's lymphomas (NHL) and the most common with an indolent presentation.[1] Patients can have a heterogeneous evolution, from asymptomatic disease without need for therapy until an aggressive course with poor chemotherapy response. The latter tends to belong in a group of progressive disease within two years of first therapy (POD24).[2] Although a better knowledge of the disease biology, there are current no clear prognostic system that can separate patients in need for aggressive treatment versus those with no need for treatment at all. But it is considered standard only treat patients with high tumor burden or symptomatic. Generally, patients that do need therapy receive CHOP/CVP or Bendamustine with additional anti-CD20 antibody. There seems to be a favorable group that can be treated with Rituximab monotherapy and remain without need for new treatment for a long period.[3] After the GALLIUM trial,[4] where Obinutuzumab was associated with 34% reduction in progression versus Rituximab, this novel anti-CD20 antibody became an option. Although a progression-free survival (PFS) benefit was demonstrated, there was no gain in overall survival (OS) at this point. Maintenance with Rituximab or Obinutuzumab is generally recommended (every 2 months for 2 years), with long term follow up from the PRIMA trial showing a sustained difference in PFS.[5] However, no OS superiority was observed. To reduce toxicity while maintaining efficacy, Lenalidomide plus Rituximab regimen was tested in untreated FL patients ("R^{2}").[6] This "chemo-free" protocol had an equal

PFS rate at 3 years compared with Rituximab plus Chemotherapy, with less hematological toxicity and neutropenic fever. The combination was also effective in the relapse setting, with a median of 40 months in PFS.[7] Chimeric antigen receptor-modified T cells (CAR-T) against CD19 is becoming widely use in lymphoma and has showed efficacy in relapse/refractory FL patients, with report of high complete remission rate and sustained remissions.[8]

Lymphoplasmacytic lymphoma (LPL): LPL is a lymphoma characterize by lymphoplasmacytic cells that produces monoclonal protein (IgM) and infiltrate the bone marrow and lymph nodes. When there is a measure IgM monoclonal production, LPL is a synonymous of Waldenström macroglobulinemia (WM). The *MYD88* L265P mutation occurs in over 90% of cases,[9] serving as a strong diagnostic marker (although not specific of WM). This mutation also has a prognostic role, with patients with the wild type showing a worse prognosis.[10] *CXCR4* is another frequent and important mutation (prevalence of 30% in WM), that together with *MYD88* can guide the treatment choice.[11] WM is an incurable disease of normally elderly patients and the treatment, when needed, focus on achieving a response (rarely complete remission) while maintaining low toxicity.[12] DRC is an option for low tumor burden and more frail patients that do not need urgent treatment. BDR serves well patients for patients with cytopenias and no neuropathy, while BR maybe prefer in bulky disease with high tumor burden.[13] Ibrutinib with or without rituximab can be used in first line[14] or relapsed patients,[15] especially with the *MYD88* mutation. Acalabrutinib and Venetoclax are other new options, with the last as one of the few active treatments in patient's refractory to ibrutinib.[16]

Marginal Zone B-cell lymphomas (MZL): The marginal zone B-cell lymphomas (MZLs) comprise extra nodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), splenic MZL (SMZL) with or without villous lymphocytes and nodal MZL (NMZL) with or without monocytoid B cells. These are three distinct clinical entities with specific diagnostic criteria, clinical and therapeutic implications.[17]

Regarding to localize H. pylori-positive gastric MZL, the initial treatment should be H. pylori eradication. This treatment can induce lymphoma regression and long-term clinical disease control in the most of 50% of the patients.[18] In patients who do not achieve lymphoma regression following antibiotic therapy, irradiation and systemic oncological therapies should be used, depending on the stage of disease. Patients who require systemic treatment, chemotherapy, immunotherapy or both are all effective.[19] SMZL in asymptomatic patients, watch-and-wait is recommended and splenectomy is considered as the recommended first treatment. Rituximab therapy alone can be indicated and has an important response rate with minimal toxicity, particular useful in patients with autoimmune disorders.[20] For asymptomatic patient diagnosed with NMZL is also recommended only observation. If systemic treatment is indicated, chemo-immunotherapy can be performed.[21]

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SP 07

Bone marrow failure

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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)