end of April 2019, 10000th patient was assigned to RMG on October 17th 2018. Median follow-up of MGUS patients is 5 years (0.0-35 years) and median follow-up for MM patients is 3 years (0.0-32 years). The huge amount of data allowed regular analysis and publication of treatment results of MM patients treated with novel drugs of multiple myeloma in the Czech Republic. The new prognostic models for MGUS progression and asymptomatic myeloma have been created based on registry data. **Conclusion:** The RMG is one of the largest MM registries with "real life" clinical data in Europe and probably worldwide. Its biggest advantage is collection of validated updated data which can be used to create rapid analyses in order to react to changing myeloma field. It helps us to create new guidelines and serves as a potent research tool. It can be also used to negotiate reimbursement process with healthcare insurance companies and government regulatory authorities for novel drugs implementation into treatment standards. Supported by project PROGRES Q40/8.

Keywords:
monoclonal gammopathies
real-world
registry

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-208

Risk of Progression Across Age and Race for Patients with Smoldering Multiple Myeloma

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Smoldering Multiple Myeloma (SMM) is the requisite asymptomatic phase that precedes MM. Observation until progression to MM has been the standard of care. However, the improvement in risk assessment and utility of chemoprevention strategies stemmed from large trials is beginning to shift the paradigm toward early detection of SMM by implementing screening strategies (e.g., PROMIS study). Lack of specific ICD code for SMM has been a major problem in epidemiologic studies aiming at characterizing the demographics and temporal dynamics of SMM. Here, we used the National Cancer Data Base (NCDB), which covers more than 70% of cancer pts in the USA. Data from year 2010 to 2014 was analyzed. We defined SMM as pts with ICD-O 9732 that were placed on active surveillance or did not receive any therapy in the first 3 months (m) after diagnosis (Ravindran et al. 2016). The effect of medical insurance on OS was estimated by Cox model after adjusting the effects of confounders including age, sex, race, tumor (primary vs. secondary), and Charlson score. There were 68234 patients with MM identified between the years 2010 – 2014, SMM consisted of 11643 patients of which 52 % were males. Seventy one percent of the patients were Whites and 24 % were Blacks. SMM was diagnosed 4 years earlier in Blacks at median age of 66 compared to 70 years old in Whites ($p<0.001$). The overall rate of progression was 21.2%. The time to progression to MM which was calculated as the time from diagnosis of SMM to time first therapy was same among Whites and Blacks. After controlling the effects of insurance, age and transplant, race was still not significant in predicting the time from diagnosis of SMM to first therapy ($p = 0.42$). Younger patients was more likely to get the first therapy (2.2 days per year increase of age, $p = 0.03$). The survival after starting therapy in SMM patients who progressed to MM was same for both the races, however patients with private insurance had longer OS ($p< 0.001$). Patients who were known to have SMM had better survival than patients with MM without known SMM which was statistically significant ($p<0.001$). Furthermore, this group of patient underwent less surgery after diagnosis of MM than patients without any known history of SMM (0.28% vs. 1.6%, $p<0.001$). There was no statistically significant difference between OS of SMM patients that never progressed to MM and general population adjusted for age and race. The rate of SMM progression to MM had a trend to be higher in Black than White but did not meet statistical significance (22.3% vs. 20.7%, p:0.069). There was a declining trend of progression rate by year of diagnosis ($p<0.001$). Taken together, our result shows higher rate of MM progression in younger SMM patients than old ones as well as earlier age of SMM diagnosis in Blacks. Also, this study highlights the importance of known SMM stage before MM in prolonging survival which can be indicative of benefit from screening programs.

Keywords:
Racial Disparity
screening
Smoldering Multiple Myeloma

Tracks:
Other Plasma Cell Disorders and Amyloidosis

SP-209

Crystalcryoglobulinemia-induced kidney disease

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Background: The spectrum of kidney damage associated with monoclonal gammopathy is wide, and notably encompasses diseases secondary to the abnormal precipitation or deposition of monoclonal immunoglobulins. Crystal(cryo)globulin-induced kidney disease is a rare but dramatic complication of monoclonal gammopathy, characterized by spontaneous crystallization of monoclonal immunoglobulins in the renal and systemic vasculature. **Case description:** We describe the case of a 69-year-old female Caucasian patient who developed purpura, skin necrosis and rapidly

progressive renal failure leading to end-stage kidney disease. Lab tests showed low serum levels of complement C3 (0.27 g/L, normal range 0.9-1.8) and C4 (0.03 g/L, normal range 0.1-0.4); a serum M-spike composed of immunoglobulin G kappa (19.9 g/L); an increased kappa to lambda free light chain ratio (5.27, normal range 0.26-1.65); and type I IgG kappa cryoglobulinemia. Urinalysis revealed microscopic hematuria and heavy proteinuria (5.35 g/day), mainly composed of albumin (95%) and of the kappa light chain. There was no hypercalcemia, anemia, nor evidence of lytic bone lesion. Complete autoimmune and viral serologic testing returned negative. Bone marrow aspiration and biopsy showed 11% monotypic κ plasma cells. On kidney biopsy, light microscopy displayed glomerular damage, with a membranoproliferative pattern of injury, and fuchsinophilic deposits on Masson's trichrome stain. Surprisingly, routine immunofluorescence staining for immunoglobulins and complement was negative, as was Congo red staining. Ultrastructural findings provided by transmission electron microscopy included crystalline material within endothelial cells and subendothelial organized microtubular deposits (thickness, 20 nm), compatible with the diagnosis of crystalcryoglobulin-induced kidney disease. **Interventions and outcomes:** The patient was started on hemodialysis and treated with plasma exchanges, and a regimen combining bortezomib, cyclophosphamide and dexamethasome (VCD). Skin lesions rapidly improved, but the patient remained dialysis-dependent. As no hematological response was achieved under VCD, a second line treatment with bortezomib, lenalidomide, and dexamethasone (VRD) was initiated. **Conclusions:** Crystal(cryo)globulinemia is a rare manifestation of multiple myeloma and results from crystallization of monoclonal immunoglobulins in the vasculature, leading to ischemia and end-organ damage. The diagnosis is challenging, as routine immunofluorescence is frequently negative (requiring pronase immunofluorescence to unmask crystallized monoclonal immunoglobulins), and relies on the identification of intravascular crystals on electron microscopy. Early intervention combining rapid removal of crystal(cryo)globulins by plasma exchanges and control of the clonal cell proliferation are warranted to reduce the burden of this rare but dramatic complication of monoclonal gammopathy.

Keywords:
monoclonal gammopathies
myeloma
Renal

Tracks:
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SP-210

Stabilization of amyloidogenic antibody light chains as a potential therapeutic strategy in AL amyloidosis

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Clonal plasma cells in multiple myeloma and related conditions secrete immunoglobulins, including free light chains. In systemic AL amyloidosis, these light chains (LCs) or their fragments can misfold and aggregate to form insoluble, non-native amyloid fibrils that cause organ damage and eventually death. Of the 3-4,000 Americans diagnosed each year with AL amyloidosis, 1,000 will die within a year of diagnosis, mainly due to heart failure. No drugs are approved specifically for AL amyloidosis, but off-label use of cytotoxic regimens approved for multiple myeloma can be effective. However, many patients are too sick at diagnosis to tolerate chemotherapy, especially those with significant cardiomyopathy. Treatments for frail AL amyloidosis patients are therefore urgently needed. Each patient has a unique light chain sequence. Only a minority of individuals with a plasma cell dyscrasia will develop amyloidosis. We therefore investigated the differences between AL-associated and non-AL-associated LCs. Full-length LCs from AL patients are less stable than other LCs, and full-length LCs remain soluble under conditions where their isolated variable domains readily aggregate. Disruption or proteolytic removal of the constant domain appears to be necessary to allow aggregation of LCs in vitro. The earliest studies on AL amyloid suggested that the variable domain forms the core of the fibril — these results have been confirmed recently by high-resolution structures of AL amyloid fibrils extracted from patients. These data all support the hypothesis that stabilization of antibody LCs could prevent misfolding, proteolysis and aggregation of LCs in patients, and be of benefit to patients. Stopping amyloid formation at the beginning by preventing precursor protein misfolding is a proven strategy to treat transthyretin amyloidosis. We therefore aim to develop drugs that can stabilize LCs and prevent amyloid deposition. This strategy is orthogonal and complementary to existing and emerging treatments for AL amyloidosis. We have identified small molecule stabilizers of the native dimeric structure of full-length LCs. A protease-coupled fluorescence polarization-based high-throughput screen identified small molecules that stabilize LCs against unfolding and proteolysis. Structural data demonstrate that at least one class of hits bind at the LC-LC dimerization interface within full-length light chains, utilizing variable domain residues that are highly conserved in most AL patients. The small molecule stabilizers identified bind to conserved residues at the variable domain—variable domain interface in the native dimer, stabilizing this putative non-toxic structure. We aim to develop more efficacious small molecules that could become drug candidates.

Keywords:
amyloidosis
light chain
therapy

Tracks:
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