Wednesday, June 04, 2008
19:00-21:00 (Marquee Parco Ciani)

Bing Center for Waldenström's macroglobulinemia update on plasma cell disorders

Chair: S.P. Treon (Boston, USA)

The role of novel agents in the management of multiple myeloma

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Natural history and management of MGUS

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Novel insights into the pathogenesis and treatment of Waldenström's macroglobulinemia

S.P. Treon (Boston, USA)

THE ROLE OF NOVEL AGENTS IN THE MANAGEMENT OF MULTIPLE MYELOMA

M.A. Dimopoulos[1], E. Kastritis[1]
[1]*Department of Clinical Therapeutics, University of Athens School of Medicine, Athens, Greece*

Alkylating agents and steroids have been the backbone of myeloma treatment for decades but in the late 90s introduction of thalidomide initiated the change in the landscape of myeloma therapeutics. Bortezomib, a proteasome inhibitor, and lenalidomide, a second generation IMiDs, followed. These novel agents have been very active in the management of relapsed / refractory myeloma and their incorporation into the treatment of these patients resulted in a significant improvement of their outcome. Phase II and III trials have also shown that thalidomide, lenalidomide and bortezomib-based regimens are superior to conventional chemotherapy in newly diagnosed patients. Thalidomide/ dexamethasone is widely used as an active induction regimen before transplantation. Bortezomib and dexamethasone is more active than VAD in patients who subsequently proceed to high dose therapy. Lenalidomide with low dose dexamethasone is also a safe induction regimen with high 1- and 2-year survival rates and favorable toxicity. In elderly patients, at least three randomized trials have shown the superiority of MP with thalidomide over MP alone. MPT is now considered the new standard treatment for patients over 65 years of age. Bortezomib combined with MP resulted in impressive response rates and halved the risk of progression compared to MP alone, in patients over 65 years. An ongoing randomized trial is comparing MP with or without lenalidomide for elderly myeloma patients. Thalidomide is effective as consolidation after transplantation especially in patients who have achieved less than a very good partial response. Ongoing studies will define the role of bortezomib and lenalidomide after high dose therapy. These novel agents also show efficacy in specific patients' subsets. Thalidomide and especially bortezomib are appropriate choices for myeloma patients with renal failure. Bortezomib and lenalidomide may overcome to a certain extent the adverse prognosis of certain cytogenetic abnormalities such as deletion 13 and t(4;14). However, special care is needed in order to avoid toxicity and not impair salvage options. Neurotoxicity of thalidomide and bortezomib needs close follow-up while thromboprophylaxis is mandated for most patients receiving thalidomide or lenalidomide based regimens. Future studies will help us further clarify the role, optimal sequence and the most active combinations of novel agents.

NATURAL HISTORY AND MANAGEMENT OF MGUS

E. Morra[1], A. Tedeschi[1], S. Miqueleiz Alamos[1]
[1]*Hematology-Oncology, Niguarda Cà Granda Hospital, Milan, Italy*

The presence of a serum monoclonal component (MC) is associated with a spectrum of lymphoid disorders including monoclonal gammopathies of undetermined significance (MGUS), lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (WM), B-cell non-Hodgkin's lymphomas (NHL; mainly low-grade histotypes), rare forms of IgM myeloma/plasmacytoma (MM) and IgM-related disorders (IgM-RDs). Monoclonal gammopathy of undeterminate significance (MGUS) is defined by a monoclonal immunoglobulin concentration in serum of 3 g/ dL or less, absence of: lytic bone lesions, hypercalcemia, anemia, renal insufficiency related to M protein, no M protein or only small amounts of monoclonal light chains in the urine and less than 10% plasma cells in the bone marrow. The true frequency of monoclonal gammopathy, particularly that of MGUS, can only be assessed by random sampling of population. The largest and most frequently cited survey found an incidence of MGUS clearly increasing with age with a prevalence of MGUS being 3.2% in persons over 50 years of age and 7.5% in those over 70. The prevalence was 4 fold higher in persons ≥ 80 years of age than those age 50-59 years.[1] The incidence of MGUS in African-Americans was greater than in Caucasians. A study of more than 4,000,000 African-Americans and white veterans in the United States reported that the prevalence of MGUS in African-Americans was 3.0 folded higher than in Caucasians. However, progression to multiple myeloma (MM) was virtually identical in both groups: 17% among African-Americans, 15% among Caucasians[2]. Aged-adjusted rates were greater in men than in women: 4.0% versus 2.7%. A population-based retrospective study was conducted for the period of1976-1997 by Ogmundsdottir et al[3]. The study was based on findings of positive electrophoresis, from all laboratories in Iceland carrying out protein electrophoresis, thus covering the entire population of the country which at that time had 270,000 inhabitants. The age-standardized incidence of MGUS detection was 10.3 and 8.6 per 100,000 for males and females, respectively. As regards the Ig isotype IgG, this forms the largest subgroup followed by IgM and IgA. The proportion reported is of 70-75% for IgG, 7-10% for IgA and 15-23% for IgM[4]. Several studies have described progression rate from MGUS to malignant plasmacell disease and factors predicting evolution. The results differ markedly depending on the population studied and time of follow-up.

The longest follow-up time study reported so far was conducted at the Mayo Clinic by Kyle et al. in a large cohort of MGUS cases.[5] During 11,009 person-years of follow-up, MGUS progressed in 115 of the 1384 patients demonstrating an average risk of the malignant evolution of almost 1 per cent each year. The study found a relative risk of 7.3 for MM, IgM lymphoma, primary amyloidosis, WM, chronic lymphocytic leukemia, and plasmacytoma in the patients with MGUS. The increased risk was found in all age groups and throughout all time intervals. The cumulative probability of progression was 12% at 10 years, 25% at 20 years, and 30% at 25 years. The initial concentration of serum monoclonal protein was a significant predictor of progression at 20 years. Similarly the rate of malignant transformation of MGUS has been estimated as 6.1-8.5% after 5 years [6,7], 5.4-19.2% after 10 years [6-10], 30-31% after 15 years and 33% after 20 years [7-10]. In our series including 1,104 MGUS patients after a median follow-up of 65 months (range, 12 to 239 months) 64 cases (5.8%) showed a malignant transformation: MM in 43 cases, WM in 12, non-Hodgkin's lymphoma in 6 cases, while the remaining 3 patients showed extramedullary plasmacytoma, primary amyloidosis and B-chronic lymphocytic leukaemia, respectively. The risk of evolution was lower in MGUS patients when compared with the group of 217 patients presenting with smouldering multiple myeloma (SMM)observed in the same

period ($P < .0001$)[15]. Several efforts have been made to identify factors that will probably predict progression from MGUS. In our series, as previously reported by other authors, age, sex, serum B_2 microglobulin levels and serum albumin levels have no prognostic value for malignant transformation. Other investigators[6,11-14] found serum paraprotein levels to be a factor influencing the probability of malignant conversion. On the contrary, in our study the multivariate analysis excluded significant relation of serum MC size with disease progression. Greater than 5% marrow plasmacytosis, detectable Bence Jones proteinuria, polyclonal serum immunoglobulin reduction, and high erythrocyte sedimentation rate (ESR) were independent factors influencing MGUS transformation. A decreased level of background Ig was detected to influence MGUS progression significantly in the study by Vuckovic et al1[14], and Baldini et al[15] identified in the presence of both uninvolved Ig reduction and BJ proteinuria a higher probability of evolution. In our MGUS series, prognostic significance of both parameters was confirmed indicating their correlation with disease activity.

Most previous studies found no influence of Ig class on disease evolution probability[7,11,12,14,15]. Although at univariate analysis the IgA/IgM MGUS correlate with malignant transformation, at the multivariate model we did not find that Ig class was an independent prognostic factor for MGUS malignant transformation. The only study in which an influence of IgA isotype on malignant transformation was detected included patients wit SMM[6].

More recently the prognostic significance of an abnormal serum free light chain ratio has been evaluated. Rajkumar et al[16] in 1,384 MGUS patients showed that the combination of a high M component (1.5 g/dL), a monoclonal protein other than IgG, and an abnormal serum free light chain ratio is associated with a high risk of progression (58% at 20 years compared with 5% when none of these risk factors were present).

Karyotyping is of no value in determining the risk of progression, because cells in metaphase are rare in MGUS. Fluorescence *in situ* hybridization is abnormal in more than half of patients with MGUS, but the prognostic impact of this finding is under investigation[17]. Another paramenter significative for prognosis in MGUS has been considered by Perez-Persona et al as the percentage of plasma cells aberrant within the bone marrow plasmacell compartment assessed by flow cytometry[18]. Few studies have been conducted to quantitate adverse outcomes ofMGUS of IgM class, which progresses to WM or other lymphomas. Kyle et al[19]. identified in Minnesota 213 patients with IgM MGUS from 1960 to 1994 and found that the relative risk of progression to lymphoma or a related disorder was 16-fold higher in IgM MGUS patients than in the general population, and that it was correlated with initial serum MC and albumin levels. In our patients with asymptomatic macroglobulinemias, we found that serum IgM levels, haemoglobin concentrations, and the presence of absolute lymphocytosis independently predicted a malignant evolution[20]. Based on results of our study[21] and on literature review we suggest that the evaluation of simple prognostic criteria such as Ig levels, marrow plasma cells infiltrate (>5%), detectable Bence Jones proteinuria, polyclonal serum immunoglobulin reduction, and high erythrocyte sedimentation rate (ESR) may permit recognition of a greater probability of malignant evolution in patients with MGUS. The new prognostic factors may be helpful to additionally discriminate between patients with higher risk of transformation. While we don't believe that a bone marrow examination or a bone survey is necessary forpatients with stable parameters, we suggest that patients at higher risk o progression should be regularly monitored.

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ADVANCEMENT IN THE DIAGNOSIS AND TREATMENT OF AL AMYLOIDOSIS

G. Merlini[1]
[1]*Amyloidosis Center, University of Pavia, Pavia, Italy*

Amyloidosis is characterized by the aggregation of normally soluble proteins into bundles of insoluble b-sheet fibrils that are deposited in target tissues. The present classification identifies amyloidoses according to the nature of the main amyloid precursor protein and up to 27 different proteins have been recognized to date to be amyloidogenic in humans. Light-chain amyloidosis (AL) is the most common form of systemic amyloidosis. It is a clonal plasma cell disorder that causes progressive multiple organ damage due to toxic light chains and fibrillar deposits. The optimal management of patients with AL amyloidosis requires early diagnosis, correct amyloid typing, effective treatment, tight follow-up and careful supportive therapy. Early diagnosis is of paramount importance and requires the histological documentation of the amyloid deposits. The correct typing of the amyloid is necessary to design appropriate treatment and can be achieved through immunohistochemistry, immunoelectron-microscopy and proteomic techniques. DNA based screening for the most common hereditary forms of amyloid may also be a helpful means of exclusion.

The prognosis depends on the severity of heart involvement, assessed using the biomarkers troponins and natriuretic peptide type B (BNP), and on response to therapy, assessed using the free-light chain (FLC) assay. The aim of therapy is to rapidly reduce the supply of the amyloidogenic monoclonal light chain by suppressing the underlying plasma cell clone. Whenever possible, patients should be enrolled in clinical trials. Several effective chemotherapy regimens are available, from high dose melphalan followed by rescue with autologous stem cells (ASCT), to high dose dexamethasone in association with oral melphalan (MDex) or with cyclophosphamide and thalidomide. A French randomized multicentric trial comparing ASCT versus MDex showed that ASCT was not superior to MDex. New agents such as lenalidomide and bortezomib in association with dexamethasone are very effective. Present findings support cyclic chemotherapy guided by frequent assessment of FLC and cardiac biomarkers, weighed cycle by cycle against treatment toxicity. The assessment of best therapy needs large, controlled, international clinical trials.

NOVEL INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF WALDENSTROM'S MACROGLOBULINEMIA

S.P. Treon[1]
[1]*Hematology-Oncology, Dana Farber Cancer Institute, Boston, United States, On Behalf of Bing Center for WM*

Numerous reports of familiar disease, including multigenerational clustering of WM and other B-cell lympho-proliferative disorders prompted us to evaluate familial WM by establishing a Familial WM Registry at our Institution. 597 patients with the consensus panel diagnosis of WM have been enrolled. 19.3% of patients were observed to have a first degree relative with either WM or another B-cell disorder including NHL, CLL, MM and MGUS. Importantly, patients with familial WM were diagnosed at a younger age, and had greater bone marrow involvement and serum IgM levels than those patients with non-familial disease. Intriguing has also been the observation that while IgM levels are often elevated in WM, IgA and IgG levels are subnormal in most patients with WM. Moreover, despite therapeutic responses including complete remissions, IgA and IgG hypogammaglobulinemia does not resolve in these patients even with long term follow-up suggesting that their deficiency may be a constitutional feature in WM with impairment of plasmacytic differentiation, heavy chain class switching or both. These findings prompted us to delineate familial predilections for WM by examining a large cohort of first and second degree family members of WM patients with and without familial histories for B-cell disorders. 145 family members were enrolled, of whom 87 were in a family with a familial history. An increased incidence of IgA deficiency (18.5% vs. 1.9%; p=0.003), elevated total IgM

(25.9% vs. 9.4%; p=0.03), and presence of a monoclonal gammopathy (22.9% vs. 1.9%; p=0.0004) were observed among family members of WM patients with a familial B-cell disorders history. Seventeen of the 19 family members with a monoclonal gammopathy within the familial cohort had an IgM monoclonal protein, and 2 had an IgG monoclonal protein. These findings prompted us to investigate expression of the APRIL/BLYS-TACI-TRAF signaling system since defects in the TACI receptor have been reported amongst patients with Common Variable Immunodeficiency Disorder (CVID) who akin to WM patients demonstrate impaired IgA and IgG production. We observed mutations in APRIL and TACI in 20% and 25% of WM patients, respectively. Importantly, significantly lower levels of IgA and IgG expression were observed for those patients with aberrancies in TACI. These findings may have particular relevance for the pathogenesis of WM since TACI knockout mice are predisposed to lymphoma development, and CVID patients have up to a 300 fold increased risk of developing lymphomas. An interesting feature of the disease is the finding of increased number of mast cells in the BM of patients with WM, most typically in association with LPC. We and others have demonstrated that BM mast cells provide important growth and survival cues to WM lymphoplasmacytic cells through multiple TNF-family ligands including CD40L, A Proliferation Inducing Ligand (APRIL), and B-lymphocyte stimulator factor (BLYS). Importantly, WM cells provide cues to mast cells for the induction of CD40L and APRIL by secretion of soluble CD27 (sCD27), a TNF-family member whose levels are significantly elevated in patients with WM and which parallel disease burden. Moreover, the SGN-70 humanized monoclonal antibody which binds to CD70 (the receptor-ligand partner of CD27), abrogated sCD27 mediated up regulation of CD40L and APRIL on WM mast cells and blocked disease progression in SCID-hu WM mice. Novel therapeutics targeting WM lymphoplasmacytic cells, mast cells and their interactions including Alemtuzumab, bortezomib (alone, and in combination), imatinib mesylate, everolimus, rituximab and thalidomide/rituximab have been investigated with significant activity. The results of these studies provide important clues into the genetic basis and pathogenesis of WM, and provide the framework for targeting WM and MC interactions in the treatment of WM.