known. Some researchers suggest that IM induced electrolyte imbalance is the reason of CK elevations. However, although our patient had PCKD and creatinine levels of 1.4 mg/dl, he had no electrolyte imbalance. To summarize, if there is myalgia or muscle weakness after the initiation of IM, then rhabdomyolysis should be suspected. In such a case, CK should be tested. In our case, CK levels and myalgia increased after IM initiation and they decreased after withdrawal. This indicates that rhabdomyolysis is secondary to IM. In IM induced rhabdomyolysis, CML treatment can be implemented as second generation TKIs such as dasatinib.

Keywords: imatinib, acute rhabdomyolysis, chronic myeloid leukemia

PP-058

MYASTENIA GRAVIS AND WALDENSTROM MACROGLOBULINEMIA: IS COMMON IMMUNOLOGIC MECHANISM POSSIBLE?

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In literature, there are some studies suggesting that the autoantibodies in plasma cell disorders rarely attack acetylcholine receptor. In this report, we shared our experience about a patient with myasthenia gravis (MG) and waldenstrom macroglobulinemia (WM).

A 24-year-old female patient consulted our hospital with fatigue that she had for 1.5 years along with nosebleed. Next, she was referred to our clinic. It was learnt that she had had a thymectomy operation because of MG and she was using piridostigmin tablets accordingly. After investigations, she was diagnosed as WM. Clinical examination revealed sensory loss. She was given R-CHOP chemotherapy and plasmapheresis due to high IGM levels. She is still on follow-up in our clinic.

In literature there are 2 cases, which has WM and MG both. Our patient is the third case. It is suggested that monoclonal antibodies can have autoantibody activities and may have relationship with auto-immune diseases. It is proposed that the IgM type antibodies in WM can sometimes react against myelin associated glycoproteins. In other studies, it was reported that in MG, most of the anti-acetylcholine antibodies were IgG, whereas it could rarely be an IgM. For this reason, in our case both diseases may have a common immunological mechanism. In the future, more studies should be conducted to expose the underlying immunological mechanisms.

Keywords: myasthenia gravis, waldenstrom macroglobulinemia, common immunologic mechanism

PP-059

TARGETING SPHINGOSINE KINASE-1/SPHINGOSINE-1-PHOSPHATE RECEPTOR 2SIGNALLING PATHWAY TO OVERCOME T315I MUTATION IN 32DCL3 CELLS

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The main problem in chronic myeloid leukemia patients is the development of resistance against tyrosine kinase inhibitors. The expression of BCR-ABL1 having T315 mutation is responsible for the development of nilotinib resistance. The alterations in sphingolipid signalling pathway is a significant BCR-ABL1-dependent resistance mechanism. Recently, we showed that sphingosine kinase-1 (SK-1)/sphingosine-1 phosphate (S1P)-mediated drug resistance is transduced via sphingosine-1 phosphate receptor 2 (S1P2) that inhibits protein phosphatase 2A (PP2A), causing increased stability of BCR-ABL1. However, specific signaling cascade involved in this process remain unkown. In this study, BCR-ABL1 expressing 32Dcl3 cells, 32D-p210Bcr-Abl(wt) and 32D-p210Bcr-Abl (T315I) were used. The antiproliferative effects of nilotinib, SK-1 inhibitor (PF-543), S1P2 inhibitor (JTE-013), phospholipase C inhibitor (U-73122) and nilotinib/PF-543 and nilotinib/JTE-013 combinations on wt and resistant cells were determined by MTT assay. Isobologram analysis was performed using CompuSyn program. The mRNA and protein levels of BCR-ABL1, SK-1 and S1P2 were checked by qRT-PCR and western blotting. Resistant cells were also transfected with Gq peptide. Vector transfected control cells do not give any response to nilotinib while IC50 values were 8 and >500 nm for wt and resistant cells, respectively. IC50 values for JTE-013 were calculated as 20 and 40 μM while that for PF-543 were 8 and 30 μM, respectively. Combination studies showed strong synergistic effects on both cell types. Although there is no significant changes in BCR-ABL1 levels for both cells, SK-1 and S1P2 levels increased in resistant cells. Combination studies caused significant decreases in BCR-ABL1 protein levels in resistant cells comparing to untreated control, PF-543 or JTE-013 treatments. Although U-73122 and Gq peptide treatments decreased BCR-ABL1 protein, their combination with okadaic acid restored BCR-ABL1 protein levels. As a conclusion, BCR-ABL1 levels decreased by activating PP2A via Gq and phopholipase C inhibition. This could be an important and novel mechanism to overcome nilotinib resistance.

PP-060

CYTOTOXIC AND APOPTOTIC EFFECTS OF FISETIN, HESPERETIN AND VITEXINON ACUTE PROMYELOCYTIC LEUKAEMIA CELLS

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Acute Promyelocytic Leukaemia (APL) is characterized by abnormal accumulation of immature granulocytes in the bone marrow and the blood stream. To date, there is no definitive treatment strategy. Fisetin, hesperetin and vitexin are flavanoids found in fruits and vegetables. Their anticancer properties have been studied on several cancer types. In this study, we aimed to examine the cytotoxic, cytostatic and apoptotic effects of fisetin, hesperetin and vitexin on Acute Promyelocytic Leukaemia cells. Cytotoxic effects were evaluated by MTT assay while apoptotic effects of these flavonoids were examined by changes in caspase-3 activity, loss of mitochondrial membrane potential (MMP) and Annexin V/PI double staining. Cytostatic effects of the flavonoids were evaluated by propidium iodide staining using flow cytometry. IC50 values of fisetin at 48 (82 μM) and 72 h (45 μM); hesperetin at 48 (190 μM) and 72 h (142 μM); and vitexin at 48 (145 μM) and 72 h (106 μM) were calculated from cell proliferation plots. 20-, 50- and 100 μM fisetin caused 1.6-, 6.2- and 11.6-fold increases in percentage of apoptotic cells, respectively. There were 1.2-, 2.1- and 3.3-fold increases in hesperetin-treated and 1.3-, 1.5- and 2.0- fold increases in vitexin-treated apoptotic HL60 cell population. 20-, 50- and 100 μM fisetin caused 1.01-, 1.15- and 1.37 fold increases in loss of MMP, respectively. Hesperetin lead to 1.9-, 2.4- and 5.4 fold increases while vitexin caused 1.1-, 1.5- and 1.6 fold changes in loss of MMP. Fisetin, hesperetin and vitexin application resulted in increases in caspase-3 enzyme activity in HL60 cells. Interestingly, fisetin, hesperetin and vitexin treatment arrested cell cycle at G2/M phase. In conclusion, we have shown for the first time that fisetin could be evaluated as the most effective flavanoid and these flavanoids could have therapeutic potentials if supported with in vivo studies.

PP-061

TET2, ASXL1, IDH1 AND IDH2 MUTATIONS IN NON-CML MYELOPROLIFERATIVE NEOPLASMS

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Introduction: Myeloproliferative neoplasms (MPNs) originate from genetically transformed hematopoietic stem cells. In recent years, TET2, ASXL1, IDH became popular due to functional and clinical consequences in MPNs. The incidence of these mutations ranges from 0 to 17%. We have studied the mutational status of TET2, ASXL1, IDH1, IDH2 (rs121913503), and IDH2 (rs267606870) in non-CML MPNs.

Results: 130 patients were enrolled to the study (M/F = 72/58). The mean age of patients was 62 (26–90). 60 (46.1%) of the patients were ET, 50 (38.5%) PV, 14 (10.8%) PMF and 6 (4.6%) were MPN unclassified. IDH (rs121913503) and IDH2 (rs267606870) mutations was not detected in the patients. IDH1 mutation was detected in 19 (14.6%) patients (16 heterozygote and 3 homozygous) (9 ET, 8 PV and 1 uMPNs). ASXL1 was detected in 67 (51.5%) patients (57 heterozygote, 10 homozygous) (31 ET, 30 PV, 6 PMF), and TET2 mutation was detected in 54 (41.5%) patients (53 heterozygote, 1 homozygous) (22 ET, 24 PV, 7 PMF). No statistically significant difference was detected between the diagnosis and the frequency of mutations. 74 of the patients had JAK2V617F mutation results (36 (48.6%) was mutated and 38 (51.4%) was normal). TET2 and ASXL1 pathogenic mutations were found in 42.1% and 61.2% of JAK2 lacking patients, respectively. Mutations in the IDH1, IDH2, TET2 and ASXL1 genes showed no association with the JAK2 mutation. Thrombosis was detected in 19 (14.6%) patients and no relationship was determined with IDH1, IDH2, TET2 and ASXL1 status.