Virtual-Hem

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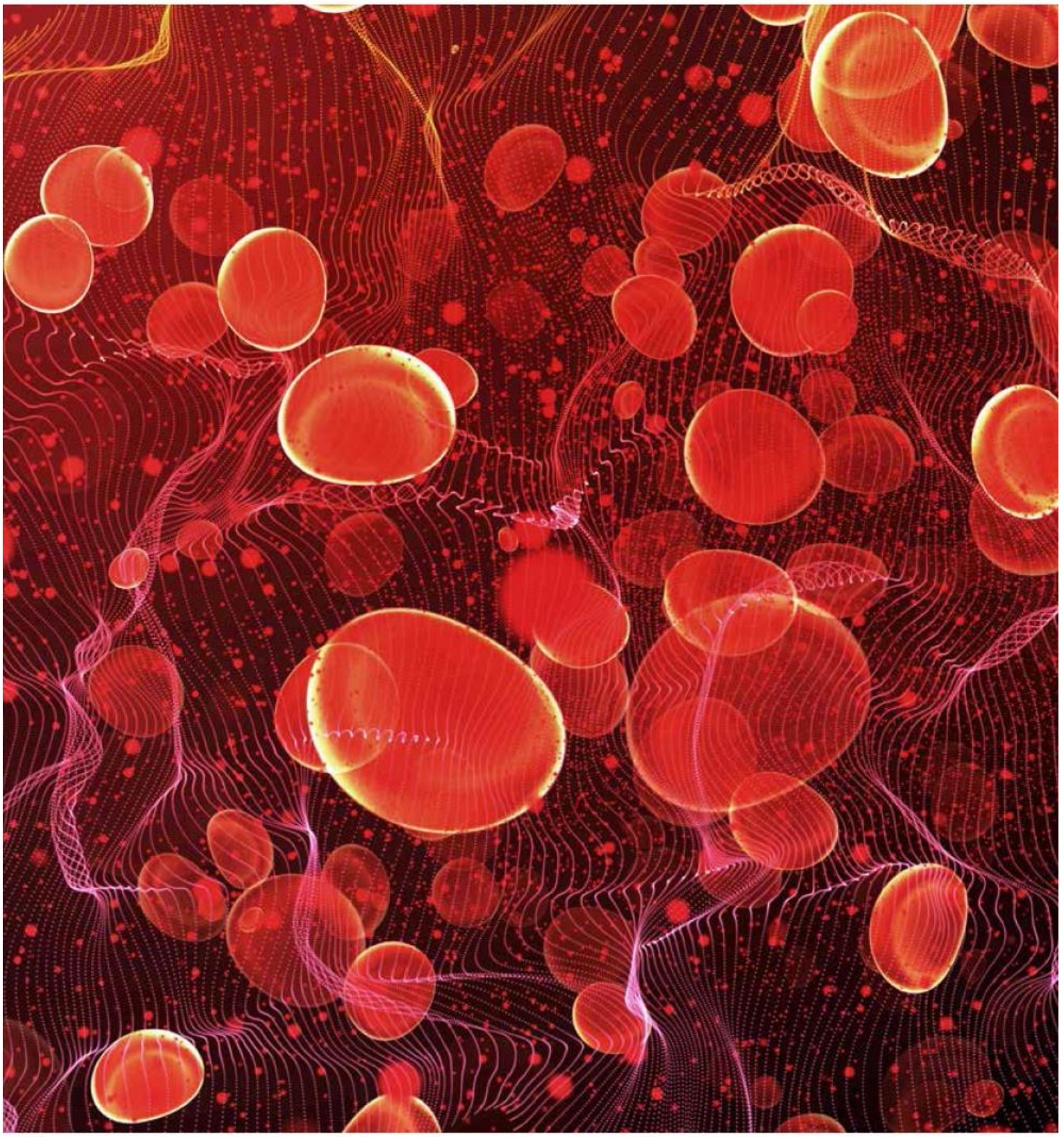
The Virtual Congress on Hematology

Age Before Beauty - An Age Adjusted Approach towards Hematological Disorders



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E-Poster 1

An Age Adjusted Approach Towards Hematological Disorders – General Aspects

Enhanced CD34+ - Hematopoietic Stem Cells Mobilization by Nutritional Supplementation with Glycosynolate of Sulforaphane, AFA Algae Extract and Curcumin in Healthy Subjects

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Several active principles from plants could trigger the release of stem cells into the circulation. CD34 is a hematological stem cells (HSC) marker. Stem cell mobilizers have shown side effects in patients.

Curcumin is the active principle from Curcuma longa extract and glycosinolate of sulforaphane is present in broccoli sprouts, which is converted into sulforaphane by mirosinase activity in humans. We analyzed whether the total number of peripheral CD34+ cell counts could be increased in healthy subjects after long-term glycosinolate of sulforaphane (66 mg/day) plus curcuminoids (120 mg/day: 38 consecutive days) nutritional supplementation in these subjects (n = 22, n = 5 subjects/group).

The total number of CD34+ cell counts were quantified by flow cytometry (CD34+ marker) in peripheral blood after long-term nutritional supplementation (38 consecutive days); these CD34 levels were compared with their own basal levels (before any supplementation) as well as data from placebo-treated subjects (n=7). This long-term nutritional supplementation could also enhance HSC mobilization under pathological conditions, including hematological diseases.

E-Poster 2

Acute Myeloid Leukemia (AML)- an Age Adjusted Approach

Obatoclax Overcomes Resistance to Venetoclax in Acute Myeloid Leukemia Cells

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Background: In acute myeloid leukemia (AML) therapy, venetoclax (ABT-199), a selective inhibitor of BCL2, has been introduced in clinical practice, presenting interesting results in unfavorable molecular markers or older AML patients when combined with epigenetic modulators. In a previous study, we characterized the sensitivity to venetoclax in four AML cellular models, being two sensitive models (MOLM13 and MV4-11), one intermediate response model (Kasumi 1), and one drug resistant model (OCI-AML3). Some molecular mechanisms involved in venetoclax resistance have been described in AML, including the overexpression of other antiapoptotic BCL2 family members (e.g. MCL1).

Objective: In the present study, we characterized the effects of obatoclax, a pan BCL2 inhibitor, in those four leukemia cell lines with different levels of sensitivity to venetoclax.

Methods: MOLM13, MV4-11 (both FLT3-ITD positive), Kasumi 1 [t(8;21), and KIT-mutated], and OCI-AML3 (NPM1- and DNMT3A-mutated) leukemia cell lines were used. Methylthiazoltetrazolium (MTT) assay was used to detect the 50% inhibiting concentration (IC50) upon exposure to increasing obatoclax concentrations (Ø; 3; 10; 30; 100; 300, and 1000 nM) for 24, 48, and 72 hours. Statistical analysis was performed by ANOVA and Bonferroni post-test using GraphPad Prism software. A p-value 0.05 was considered significant.

Results: All AML cell lines presented a dose and time-sensitivity to obatoclax, displaying IC50 values in low nM range (MOLM13: 160, 6, and 4 nM; MV4-11: 46, 17, and 6 nM; Kasumi 1: 845, 329, and 8 nM; OCI-AML3: 382, 29, and 12 nM for 24, 48, and 72 hours of exposure to obatoclax, respectively, all p0.05 compared to vehicle-treated cells).

Conclusion: Our results data indicated that obatoclax reduces cell viability in AML cells, independently of their sensitivity to venetoclax, suggesting that pan-BCL2 inhibition by this drug may overcome intrinsic resistance in AML cellular models. Supported by FAPESP, CAPES, and CNPq.

E-Poster 3

An Age Adjusted Approach Towards Hematological Disorders – General Aspects

Hematological Parameters Linked with Age in Coronavirus Patients in Pakistan

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Background: The present study focus on hematological parameters linked in the patients suffering from coronavirus in Pakistan. COVID-19 is a new human infectious disease.

Objectives: Blood tests have an important role in early diagnosis of the disease, considering the information they provide to physicians regarding the inflammatory process. This information includes leukocyte count and characteristics such as neutrophil- or lymphocyte-dominance, inflammation, collateral organ damage and the severity of the disease. Biomarkers provide information regarding the nature of pneumonia, meaning that physicians can determine whether a disease is bacterial or due to other etiologies by analyzing blood test results.

Methods: The definitive diagnosis of COVID-19 was made by RT-PCR analysis, but this was a time-consuming and less accessible test. With this test, the time it takes to diagnose and treat patients can be delayed. Low values of leukocytes, neutrophils, platelets NLR and SII and high values of hemoglobin found with a CBC to the initial diagnosis of COVID-19.

Results: With a population of around 220 million, it is estimated that Pakistan has between 170,000 and 200,000 new cancer cases each year. The first cases of coronavirus surfaced in Pakistan in late February, 2020. Further increases were seen through March, 2020 as Pakistanis overseas. As the illness progressed, neutrophilia emerged in several cases, and patients with severe critical pulmonary conditions showed higher neutrophils than common type. Thrombocytopenia was resulting from the consumption and/or the reduced production of platelets in damaged tissues. The activation of monocyte-macrophage system aggravates the immune damage other tissues, prothrombin time and platelet consumption.

Conclusions: COVID-19 is a new human infectious disease caused by a novel coronavirus SARS-CoV-2. Hematological abnormalities are not rare in COVID-19 patients including lymphopenia, neutrophilia, thrombocytopenia, and decline of hemoglobin. The effects of SARS-CoV-2 on hematopoiesis are still poorly understood, which deserves further exploration.

E-Poster 4

Acute Myeloid Leukemia (AML)- an Age Adjusted Approach

Characterization of Cellular and Molecular Antileukemic Activity of a New Synthetic Cyclopenta[b]indole in ATRA-sensitive and Resistant Acute Promyelocytic Leukemia Cell Models

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Background: Acute promyelocytic leukemia (APL) is associated with PML-RARα oncogene, which is target using ATRA-based chemotherapy. Treatment resistance is rare, but when occurs, it represents a clinical challenge.

Objective: Using NB4 (ATRA-sensitive) and NB4-R2 (ATRA-resistant) cells, to investigate the effects of synthetic cyclopenta[b]indoles on leukemia phenotype.

Methods: Three synthetic cyclopenta[b]indoles previously optimized were used. Previous results from our research group indicated that these compounds bind to and inhibits microtubule dynamics. Cell viability was assessed by MTT, clonogenicity by colony formation assay, apoptosis by annexin-V/7AAD staining and flow cytometry, cell cycle by propidium iodide staining and flow cytometry, and cell morphology by H&E staining and optical microscopy. Microtubule polymerization were evaluated using the in vivo tubulin polymerization assay. Molecular markers of proliferation (STMN1), apoptosis (PARP1), and DNA damage (p-H2AX) were investigated by Western Blot. Statistical analyzes were performed by ANOVA test and Bonferroni post-test.

Results: Among three synthetic cyclopenta[b]indoles tested, the compound 2 that presented higher cytotoxic activity was better characterized. In NB4 and NB4-R2, compound 2 displayed time-dependent cytotoxic activity in µM range, significantly decreased the clonogenicity upon 24 hours of exposure, increased apoptosis and cell cycle arrest at S/G2/M phase cells upon 48 hours of treatment. Morphological analysis indicated aberrant mitosis, which corroborates cell cycle findings. In the molecular scenario, compound 2 reduced STMN1 expression and activity, and induced PARP1 and H2AX phosphorylation, indicating reduction of cell proliferation, apoptosis and DNA damage. Furthermore, in tubulin polymerization assay, NB4 and NB4-R2 cells showed a large reduction in the polymerized tubulin levels after exposure to compound 2, which indicates tubulin as a target, supporting previous results from our group.

Conclusion: Synthetic cyclopenta[b]indoles reduced cell viability in ATRA-sensitive and ATRA-resistant APL cells potentially targeting microtubule dynamics and leading to mitotic collapse and cell death.

E-Poster 5

Acute Myeloid Leukemia (AML)- an Age Adjusted Approach

Pharmacological Inhibition of Ezrin Reduces Cell Viability and Clonogenicity in Acute Myeloid Leukemia Cells

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Background: Acute myeloid leukemia (AML) is the most common type of leukemia in adults and despite great advances in understanding the molecular basis of the disease, therapeutic options for AML remain very limited, with patient survival rates being low, due to the high prevalence of resistance or relapse to chemotherapeutic drugs used in clinical practice. Recently, our research group identified the EZR gene, which encodes the ezrin protein, as an independent marker of unfavorable prognosis in patients with AML. Ezrin is an important protein associated with the cytoskeleton that allows signal transduction between membrane proteins and actin filaments.

Objectives: To verify the impact of the pharmacological inhibition of ezrin on the viability and autonomous clonal growth of AML cell lines.

Material and Methods: Leukemia cell lines, MOLM13 (FLT3-ITD) and Kasumi 1 (KITN822K), were treated with increasing concentrations of ezrin inhibitors, NSC305787 and NSC668394. Cell viability was assessed by the MTT assay and autonomous clonal growth by cultivation in growth factors-free methylcellulose. Statistical analyzes were performed using the ANOVA test and the Bonferroni post-test, and a value of p0.05 was considered statistically significant.

Results: The treatment with both ezrin inhibitors was able to significantly reduce the cell viability of MOLM13 and Kasumi 1 cells in a concentration-dependent manner (p0.05). The compound NSC305787 displayed (IC50 ranged 1 - 1.5 µM) greater potency and effectiveness than NSC668394 (IC50 ranged 6.7 - 26 µM). Long-term treatment with NSC305787 and NSC668394 reduced the clonogenicity of MOLM13 and Kasumi 1 cells in a concentration-dependent manner (p0.05).

Conclusion: Our results indicate that ezrin inhibitors, NSC305787 and NSC668394, have antileukemic effects: reduced cell survival, and autonomous clonal growth which is a poor prognostic factor in patients with AML. Supported by FAPESP, CAPES, and CNPq.

E-Poster 6

Acute Lymphoblastic leukemia (ALL) - an Age Adjusted Approach

AD80 Inhibits the PI3K/AKT/STMN1 Axis and Exhibits Antineoplastic Effects in Acute Leukemia Cellular Models

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Acute lymphoblastic leukemia (AL) is characterized by exacerbated clonal proliferation of immature hematopoietic progenitors presenting high relapse and mortality rates. Stathmin 1 (STMN1) is a phosphoprotein highly expressed and induces cell proliferation and autonomous clonal growth in AL.

Objectives: The present study aimed to evaluate cellular and molecular effects of inhibition Stathmin1.

Methods: Jurkat and Namalwa, acute lymphoblastic leukemia cells, and NB4 and U937, acute myeloid leukemia cells were used. Cell viability was assessed by MTT, apoptosis by annexin V/7AAD labeling, cell cycle by propidium iodide labeling and flow cytometry (CF), clonogenicity by autonomous colony formation, and protein expression and phosphorylation by Western blot. Statistical analysis was performed by ANOVA test and Bonferroni post-test. A p0.05 was considered significant.

Results: AD80 reduced cell viability, and induced apoptosis, G2/M cell cycle arrest, reduced autonomous clonal growth in a dose- and time-dependent manner in leukemia cells (p0.05). In the molecular scenario, AD80 reduced STMN1 expression and also induces PARP1 cleavage and γH2AX expression. In addition, AD80, effectively inhibits S6 Ribosomal Protein phosphorylation (an effector of PI3K/AKT signaling) and Survivin (BIRC5) expression in both leukemia cell lines tested.

Conclusion: AD80 inhibited STMN1 signaling and display antineoplastic effects in acute leukemia cellular models, reducing clonogenicity, survival, and cell cycle progression. Supported by CNPq, CAPES and FAPESP (2017/24993-0, 2018/19372-9, 2018/15904-6, and 2015/17177-6).

E-Poster 7

Lymphoproliferative Disorders (LPD) and Plasma Cell Dyscrasias (PCD)- an Age Adjusted Approach

Implication of Thyroid Status on Proliferation of T Lymphoma: The Usefulness of Murine Models in the Study of Tumor Progression

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Background: We previously demonstrated that thyroid hormones regulate the growth of T lymphoma lines, but the underlying mechanisms of action have not been elucidated. Murine models have been very useful for the study of numerous diseases. Here, we use murine models of hyperthyroidism and hypothyroidism to analyze the role of thyroid status on tumor development.

Objective: To study the effect of thyroid status on cell cycle regulatory proteins.

Methods: Female C57BL/6J mice were treated with placebo, with thyroxine (0.012 mg/ml; 30 days) or with propylthiouracil (0.5 mg/ml; 15 days) and were inoculated subcutaneously with EL-4 T lymphoma cells. Tumor volume was measured daily using calipers. Survival analysis was determined using Kaplan-Meier curves. Proliferation and apoptosis markers were examined by immunohistochemistry. The proliferation kinetics was quantified by CFSE-staining. The expression of cell cycle proteins was analyzed by qPCR and Western blot.

Results: Hyperthyroid animals exhibited a higher tumor volume that was correlated with a higher rate of cell division and reduced survival. Tumor tissue from hyperthyroid animals had a higher expression of PCNA and caspase 3. Hypothyroid mice did not differ significantly from the euthyroid controls with respect to these parameters. The levels of cyclins D1 and D3 were increased in the tumors from hyperthyroid mice, while the cell cycle inhibitors p16/INK4A and p27/Kip1 and the tumor suppressor p53 were increased in hypothyroid mice.

Conclusions: The thyroid status modulates the growth of EL-4 T lymphoma *in vivo* by regulating the expression of cyclins, cyclin-dependent kinase inhibitors and the tumor suppressor p53.

E-Poster 8

Lymphoproliferative Disorders (LPD) and Plasma Cell Dyscrasias (PCD)- an Age Adjusted Approach

Angiogenesis in a T-Lymphoma Growing as a Solid Tumor in Hyperthyroid and Hypothyroid Mice: A Phenomenon Modulated by Thyroid Status

Helena Sterle[1], Eduardo Valli[1], Diego Martinel Lamas[1], Alicia Klecha[1], Lucas Colombo[2], Vanina Medina[1], Graciela Cremaschi[1], **María Laura Barreiro Arcos**[1]

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Background: Angiogenesis is a physiological process that occurs during embryogenesis, tissue repair, and the development of solid tumors. The thyroid status modulates angiogenesis in various tissues, but its role in tumor angiogenesis has not been elucidated.

Objective: To study the effect of thyroid status on the angiogenesis and proliferation of El-4 T lymphoma growing as a solid tumor in murine models of hyperthyroidism and hypothyroidism.

Methods: Female C57BL/6J mice were treated with placebo, with thyroxine (0.012 mg/ml; 30 days) or with propylthiouracil (0.5 mg/ml; 15 days) and were inoculated subcutaneously with EL-4 cells. Tumor volume was measured daily using calipers. The proliferating cell nuclear antigen (PCNA) was quantified by immunostaining and the rate of cell division was determined by staining with CFSE-DA. Vascularization in tumor tissue was evaluated using the Masson's trichrome staining and immunostaining with an anti-CD31 antibody. Blood vessels supplying the tumor were analized by microscopy.

Results: Hyperthyroid animals exhibited a higher tumor volume that was correlated with a higher rate of cell division. Tumor tissue from hyperthyroid mice had increased levels of PCNA expression. Tumors from hyperthyroid animals exhibited more vascularization, with large vessels and increased expression of the vascular endothelium marker CD31. Hyperthyroid mice had a higher level of peritumoral angiogenesis. Tumors from hypothyroid mice did not show significant differences with respect to the controls.

Conclusions: The hyperthyroid state induces the growth of new blood vessels that supply the tumor, favoring a greater tumor development. The hypothyroid state has no effect on intratumoral or peritumoral angiogenesis.

E-Poster 9

Lymphoproliferative Disorders (LPD) and Plasma Cell Dyscrasias (PCD)- an Age Adjusted Approach

Expression of RUVBL1 Component of R2TP Complex Correlates with Poor Prognosis in DLBCL.

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Background:

DLBCL is the most prevalent subtype of non-Hodgkin's lymphoma (NHL) accounting for 30% of adult NHL worldwide. Recently identified HSP-90 co-chaperone complex R2TP has been shown to contribute towards DNA damage and Myc induced transformation which are well known in DLBCL. The aim of this study was to compare the immunohistochemical expression of R2TP complex components RUVBL1, PIH1D1 and RPAP3 in FFPE DLBCL patients. Surprisingly, the overexpression of RUVBL1 component of R2TP complex turned out to be associated with relapse and poor survival.

Objective:

To check the immunohistochemical expression of the components of R2TP complex and their correlation with the patient survival.

Methods:

Immunohistochemical staining of R2TP complex components RUVBL1, PIH1D1 and RPAP3 was performed on FFPE tissue samples of 54 tumours patients of. The immunohistochemical staining was assessed by two pathologists who were blinded to all clinicopathological and cytogenetic details. Based on a scoring system, expression of these components was graded as high or low.

Results:

There were total of 54 tumour tissues out of which 32 (59.26%) cases strongly stained for RUVBL1 and none of the reactive lymph node stained for RUVBL1. The RUVBL1 expression was correlated with the clinicopathological features and positive statistical significance was observed with progression free survival (p=0.0146); overall survival (p=0.0328) and bone marrow involvement (p=0.0525). Kaplan-Meier survival analysis showed a statistically significant difference in progression free survival those in RUVBL1 positive and negative (21 vs 39 months, respectively, p=0.008).

Conclusion:

RUVBL1 over expression in DLBCL is associated with relapse and poor survival.

Acute Myeloid Leukemia (AML)- an Age Adjusted Approach

Acute Myeloid Leukemia with Minimal Differentiation with Translocation t(16;21)(p11;q22): Case Report and Review of the Literature

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The t(16;21)(p11;q22) carry the FUS-ERG fusion genes. This translocation has been described in acute myeloid leukemia (AML) as well as solid tumors, characterized by exhibit poor prognosis and a high relapse rate. In this study, we report a 54-years-old Peruvian female patient diagnosed with Acute Myeloid Leukemia with Minimal Differentiation (M0: French American British Classification: FAB) with 23% of blast in bone marrow. Immunophenotype of blast cells express positive markers: CD13, CD71, CD34, CD33, CD45, CD56; negative for: CD64, HLA-DR, CD14, cMPO, CD15, CD7, and variable expression for: CD17, CD117, CD11b. Cytogenetic analysis: t(16;21)(p11;q22) in all metaphases. The patient was induced to chemotherapy based on DAUNOMICIN (40 ug/m2) and CYTOSINE ARABINOSIDE Ara-C: (200 m/m2), remaining in complete remission one month after treatment, but relapsed in the third month. She finally died four months after starting treatment. In the literature, were selected fourteen different AML cases from Mitelman database (https://mitelmandatabase.isb-cgc.org/) with immunophenotype reports and the t(16;21)(p11;q22). The immunophenotypic and morphological characterization of the fourteen cases (n=14) reviewed correspond to aberrant cells of the myeloid lineage, M1(6/14), M2(2/14), M4(3/14), M5 and M7(1/14) according to FAB classification. Three cases (3/14) were pediatric patients (median age: 7 years-old) and eleven cases (11/14) were adult patients (median age: 38 years-old), the predominant sex affected was female (10/14) with a 0.4 ratio (Male/Female). In the flow cytometry analysis: 10/14 exhibit a variable positive expression for CD56, as our patient in the report, correlating with unfavorable prognosis. Our case compare with literature, show strongly expression of CD13, CD33, CD34, CD56 and coexpression of CD117, on another hand less common expressed was CD11b, despite the fact that no phenotype was classified as M0. In conclusion, the AML M0 corresponding to 5% of AML, additionally the CD56 expression and the rare t(16;21)(p11;q22) in our patient leads to a poor prognosis.

E-Poster 11

Chronic Myeloid leukemia (CML) and Myeloproliferative Disorders (MPD)- an Age Adjusted Approach

Identification of New Bcr-Abl/USP1 Protein Complex and the Effect of USP1 Deubiquitinase on the Expression Level of Bcr-Abl Oncoprotein in K562 Cells

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Background: Bcr-Abl oncoprotein causes the development of chronic myeloid leukemia (CML). As a result of mass spectrometric analysis, ubiquitin-specific protease 1 (USP1) was identified as one of the potential candidates for interaction with PH domain of Bcr-Abl. We hypothesize that during the formation of Bcr-Abl/USP1 protein complex, USP1 deubiquinates the oncoprotein, which prevents its proteosomal degradation and causes it to accumulate in cells leading to disease progression.

Objective: Investigation of Bcr-Abl/USP1 protein complex and determination of the effect of USP1 activity on expression level of oncoprotein in CML cells.

Method: The studies were performed using co-immunoprecipitation, Western blotting, immunofluorescence staining, confocal microscopy, statistical analysis. Deubiquitinase USP1 was inhibited by compound ML323.

Results: The interaction of oncoprotein Bcr-Abl and deubiquitinase USP1 was determined by coimmunoprecipitation. The immunofluorescence method followed by confocal microscopy showed a high level of colocalization between Bcr-Abl and USP1 proteins in nuclei of K562 cells, which decreases after incubation with ML323. Inhibition of the deubiquitinase activity of USP1 reduced the level of Bcr-Abl oncoprotein in K562 cells.

Conclusion: A new Bcr-Abl/USP1 protein complex was identified and it was found that the site of its formation is nuclei of K562 cells. The effect of USP1 deubiquitinase on the level of oncoprotein in CML cells was revealed. Thus, the obtained results create preconditions for the development of a new CML treatment strategy using target protein capable of selectively reducing the level of Bcr-Abl oncoprotein and effectively overcoming the resistance to kinase inhibitors.

E-Poster 12

Chronic Myeloid leukemia (CML) and Myeloproliferative Disorders (MPD)- an Age Adjusted Approach

BCR and Cortactin Colocalize with Centrosomes Indicating Potential Role in Centrosome-Mediated Actin Branching.

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Background. Chromosomal translocation between 9 and 22 leads to fusion of bcr and abl genes. Because of different breakpoints in bcr gene three forms of chimeric BCR-ABL proteins exist – p230, p210, and p190. BCR-ABL-p190 lacks Pleckstrin homology (PH) domain of BCR and is associated with acute lymphoblastic leukemia (ALL). In contrast, BCR-ABL-p210 has PH domain and occurs during chronic myeloblastic leukemia (CML). Previously cortactin was identified as potential interaction partner of BCR-ABL by mass-spectrometry. Main function of cortactin is actin branching. It was previously shown that BCR-ABL can bind to centrosomes. Centrosome regulates cell division and acts as actin organizing centre. It was unknown whether BCR and cortactin can bind to centrosomes in tandem and whether they can affect its' function.

Objective. Determine whether cortactin and BCR colocalize with centrosomes.

Methods. Immunofluorescence, fluorescence confocal microscopy, live cell imaging, transfection.

Results. We discovered that cortactin and BCR colocalize with centrosome of live HEK293T cells stained with SiR-tubulin stain. BCR colocalizes with gamma-tubulin in fixed K562 cells and localizes at points of actin branching.

Conclusion. BCR-ABL through its' abnormal tyrosine-kinase activity together with cortactin may have disrupting effect on centrosomes resulting in abnormalities in cell division and proliferation. These results may be a background to alternative CML treatment approaches through inhibition of cortactin-specific signalling pathways.

E-Poster 13

Chronic Myeloid leukemia (CML) and Myeloproliferative Disorders (MPD)- an Age Adjusted Approach

Discontinuation of Tyrosine Kinase Inhibitors (TKI) in Patients With Chronic Myeloid Leukemia (CML) After First Complete Molecular Remission in Routine Clinical Practice

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Background

TKI fundamentally improved survival rates of CML patients. Decision to discontinue TKI may be related to adverse effect, impact on quality of life, cost or even with the decision to conceive. However, this remains a challenge for healthcare professionals. A number of studies have been conducted to demonstrate the possibility of TKI cessation in well responding patients.

Objective

We retrospectively analyzed the data in 37 CML patients who discontinued TKI therapy at our institution.

Method

TKI treatment was discontinued in 25 female and 12 male patients (20 imatinib, 15 nilotinib, 2 dasatinib). Median age at diagnosis was 47 years (range 9-82). 33 patients (32%) were receiving their second or third line treatment. All patients achieved complete cytogenetic remission (CCyR), whereas MR4.5 was obtained in 35 patients (94%). Thirty-one patients (86%) discontinued therapy electively due to sustained deep molecular response (DMR), 2 due to intolerance, 1 for financial reason, 1 due to occurrence of multiple sclerosis and 1 after diagnosis of a secondary cancer. At the time of discontinuation, median MR4.5 duration was 48 months (range 5-163). After a median follow-up of 18 months since discontinuation, 15 patients (40%) experienced loss of MMR at a median of 4 months (range 3-24; 4 after 6 months). Patients receiving imatinib, nilotinib and dasatinib lost their response at a rate of 40%, 46% and 0% respectively. Relapse rate for patients with stable MR4.5 2 years was 34% (10/29), while it was 50% (3/6) for those with 2 years. All relapsing patients were retreated and 80% (22/37) achieved MMR at a median of 4 months.

Conclusion

Our data show that some patients with deep responses (60% from our cohort) can achieve treatment free remission (TRF). As retreatment is usually successful after loss of MMR, discrimination of higher risk patients for resistant relapse needs to be elucidated.

An Age Adjusted Approach Towards Hematological Disorders – General Aspects

Risk of Hematological Disorders after Radioactive Iodine Therapy for Well Differtentiated Thyroid Carcinoma: an Age Adjusted Approach

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Background: Radioactive iodine administration (RAI) following total thyroidectomy has been traditionally recommended for the adjuvant treatment of all patients diagnosed with well differentiated thyroid carcinoma. However, recent evidence suggests absence of data on survival improvement of patients with low risk or intermediate risk of well differentiated thyroid carcinoma. Thus, guidelines recommend a risk adapted decision on the RAI treatment of patients with well differentiated thyroid carcinoma. RAI treatment is associated with the risk of development of hematological disorders including acute leucemia, chronic myeloid leucemia, multiple myeloma, myelosuppression, aplastic anemia. This risk should be taken into account in the decision process for RAI treatment in patients presenting with well differentiated thyroid carcinoma, especially in the case of young patients.

Objective: This manuscript aimed to review data on the risk of hematological disorders after radioiodine treatment for well differentiated thyroid carcinoma in an age adjusted approach.

Methods: Pubmed, Scopus,Google Scholar, Science Citation Index were searched with the search terms “radioactive iodine administration”, “RAI treatment”, “well differentiated thyroid carcinoma”, “acute leucemia”, ‘chronic myeloid leucemia’ ‘multiple myeloma’ ‘hematological malignancies’ ‘hematological disorders, “age adjusted”. The search covered the period up to and including August 2020. The main outcomes was the risk of hematological disorders after RAI treatment in patients with well differentiated thyroid carcinoma. Only full publications were considered.

Results: Evidence suggests that RAI is associated with an increased risk of acute myeloid leucemia and chronic myeloid leucemia especially at high doses. However, there are reports of multiple myeloma even after low dose RAI treatment. Myelosuppression and aplastic anemia have also been reported after RAI treatment of well differentiated thyroid carcinoma. Patients, especially children and young patients should be followed in a lifetime perspective for the prompt diagnosis of these disorders.

Conclusion: The risk of hematological disorders should be taken into account in the decision process for RAI treatment in patients with well differentiated thyroid carcinoma in an age adjusted approach.

E-Poster 15

Chronic Myeloid leukemia (CML) and Myeloproliferative Disorders (MPD)- an Age Adjusted Approach

Viral-Specific Immune Cell Responses During Immune Reconstitution after Various Hematopoietic Stem Cell Transplantation Types

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Background. The frequencies of reactivation of latent viral infections in umbilical cord blood recipients (UCB) higher than in matched sibling donor (MSD) after hematopoietic stem cell transplantation treatment for leukemias. It is accompanied by a significant delay in quantitative recovery of T cell subsets, however, faster quantitative recovery of B and natural killer subpopulations in the UCB group, throughout a year of post-transplantation.
Methods. We used Interferon-gamma (INFG) and Granzyme B (GZMB) ELISpot assays to quantify the frequencies of immune cells that secrete cytotoxic molecules in response to stimulation with ten peptides, from five most commonly reactivated viral infections, at four time points after transplantation. Half of the patients in each group were CMV seronegative and another half were CMV seropositive. Half of UCB CMV+ patients developed CMV reactivation, as detected by CMV DNAemia, and none of CMV+ MSD recipients reactivated.
Results. The quantities of the IFNG producing cells increased during a year of observation in all CMV+ groups, however, there was a significant delay in recovery of the response toward antigens in CMV+ reactivated UCB subgroup. Conversely, the secretion of the Granzyme B, in CMV+ subgroup was significantly higher at all time points. A strong positive correlation was observed between low ratios of effector T cells/NK cells, and IFNG/GZMB, in UCB recipients who exhibit viral reactivation.
Conclusion. This comparative analysis revealed delayed kinetics of quantitative immune recovery and viral-specific immune cell responses in UCB patients that were associated with the increased incidence of reactivation of latent viral infections.

Chronic Myeloid leukemia (CML) and Myeloproliferative Disorders (MPD)- an Age Adjusted Approach

Stimuli-Responsive Polymeric Nanoparticles for Sustained Targeting of BCR-ABL+ LEUKEMIA STEM CELLS

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Packaging small-molecule drugs into biodegradable polymeric nanoparticles could impact cancer therapy, by increasing drug bio-availability. We focused on chronic myeloid leukaemia (CML) which represents the first clonal malignancy effectively treated with a tyrosine kinase inhibitor (Iimatinib, IM). IM induces complete cytogenetic responses in more than 85% of patients. However, over 20% of initial responders discontinue treatment due to lack of efficacy or other adverse effects. Second- and third-generation inhibitors may address TKI resistance. However, whilst TKIs are highly effective on leukemic myeloid progenitor cells, they are unable to eradicate Leukemic Stem Cells (LSCs), which are BCR-ABL1- independent. This eventually causes disease progression and has stimulated the search for additional LSC-specific therapeutic targets. This therefore prompted us to validate whether polymeric nanoparticles could overcome inherent resistance of CML stem cells to IM, also representing efficient tools for ex vivo purging of malignant progenitors from patient autografts. In the last few years, we have validated different types of polymeric nanoparticles (NPs) for IM and Nilotinib delivery to CML cells. To sum up, our pilot studies showing the clinical application of biodegradable NPs as feasible, specific, safe and effective ex vivo purging agents to target resistant leukemic stem cells, thereby optimizing transplant outcome of CML patients or reducing IM dose escalation.