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Research Article

Abnormal Apoptosis of Autoimmunity from Chronic Lymphocytic Leukaemia

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A B S T R A C T

Introduce: Apoptosis, with roll in the scheduling of cell life, is a normal process different from cell necrosis, which occurs due to physical or chemical aggression. The decision to activate a suicide process is made based on intrinsic or extrinsic apoptotic messages. The extrinsic ways which inducer apoptosis are ligands and cytokines for death receptors, (DR-Death receptors), being on each cell surface. The intrinsic ways which inducer apoptosis come from the mitochondria or nucleus. Proapoptotic signals, which promote or cause apoptosis, participate in a cascade that leads to the culmination cleavage of a set of proteins, resulting in the disassembly of the cells for apoptosis.

Aim: The scope of this review is to emphasise that massive apoptosis overloading the phagocytic capacity can trigger an autoimmune reaction through the presentation of nucleosomes to the immune system.

Methods: A large cohort study of cases with the primary Chronic Lymphocytic Leukemia, (CLL), examined samples from more than 100 patients for response to MDM2 protein inhibition and found a direct correlation between wild-type P53 status and MDM2 inhibitor, Nutlin-3, which induced a cytotoxicity across various CLL subtypes.

In experimental models, disrupting the MDM2–p53 protein interaction restored p53 function and sensitized tumours to chemotherapy or radiotherapy. This response was not presented in malignant B cells lymphocytes having the expression of ZAP-70 receptor membrane, the expression of CD38 receptor with un-mutated immunoglobulin variable genes and with IGHV and mono-allelic ATM gene loss.

Results: Pro-apoptotic signals apoptosis receptors, such as TNF-related apoptosis-inducing ligand, (TRAIL), Tumour Necrosis Factor, (TNF) and Fas receptor, also known as APO-1 or CD95 receptors are the key adaptor proteins transmitting apoptotic signals mediated by the main death receptors, (DRs), known to induce and autophagy process. Also, the autoimmune cytopenia, (AIC), appeared in patients with high-risk CLL (ex, unmutated immunoglobulin heavy chain variable region gene, [IGHV], 17p and 11q deletion).

Conclusions: Presented research are impact on the clinical management of patients and requires an attitude adjustment therapeutic adequate in a personalized medicine.

Keywords: P53 Gene; Apoptosis; Fluorescence in Situ Hybridization; Tumour Necrosis Factor; Death receptors

Introduction

Chronic lymphocytic leukemia, (CLL), is frequently associated with immune disturbances.

Aim of this study was to emphasis the mechanisms which lead to autoimmune cytopenia in CLL and involvement of interactions between the malignant B-CLL cells, together with abnormally functioning B cells in the cellular microenvironment **(Figure 1)**.

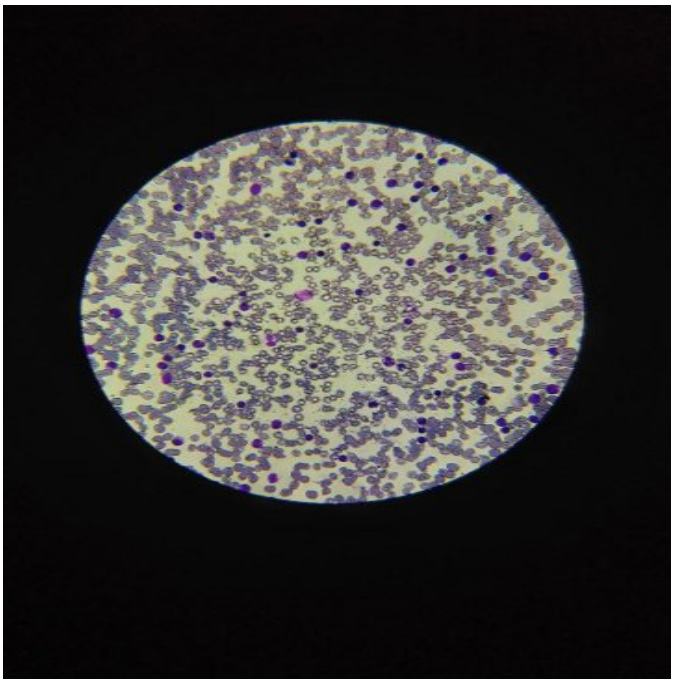

Figure 1: Image of the microscopic smear in Chronic Lymphocytic Leukemia: numerous lymphocytes presenting a nucleus with an irregular contour, arranged in isolation on the peripheral blood slide and frequence relative of nuclear shadows Gumprecht.

Apoptosis is characterized by the apoptotic pathways, starting from the activation of the death receptor, (DRs), which is followed by a downstream signalling cascade including the involvement of mitochondria, subsequent caspase activation and DNA cleavage. However, pro-apoptotic signals apoptosis receptors, such as TNF-related apoptosis-inducing ligand, (TRAIL), Tumour Necrosis Factor, (TNF) and Fas receptor, also known as APO-1 or CD95 receptors are the key adaptor proteins transmitting apoptotic signals mediated by the main death receptors, (DRs). Pro-apoptotic signals, which promote or cause apoptosis, participate in a cascade and leads to the culmination cleavage of a set of proteins, resulting in the disassembly of the cells for apoptosis, [1].

Some auto-reactive cells may escape natural apoptosis and represent continuous treatment with a potential autoimmune response. However apoptotic cells do not disappear after phagocytosis. Ingredients of apoptotic cells indeed survive the intracellular processing and are recycled to the membrane of phagocytes. Massive apoptosis overloading the phagocytic capacity may trigger an autoimmune reaction through the presentation of nucleosomes to the immune system, [2].

In the last years, were extensive studies in various mature B cell malignancies, including CLL, with isoform p53 protein, products of mutant P53 gene, in hematologic malignant diseases with the chromosomal short 17-p. Identifying different P53 gene mutations is very important because these mutations have an impact on the patient's clinical course in CLL with the p53 protein mutant isoform.

The most important regulatory mechanisms of autoimmunity and oncogenesis process are death receptors, caspases, mitochondria, the Bcl-2 family proto-oncogenes and tumour suppressor gene P53. Mitochondria would provide an ideal molecular platform of counter regulation of autophagic cell death vs. apoptotic cell death. In this regard, mitochondria-associated proteins may also be responsible for interactions between the autophagic and apoptotic pathways. Mitochondria are shown to be playing an important role in the induction of apoptosis through the cytochrome C release via the disruption of mitochondrial outer membrane potential, **(Figure 2)**.

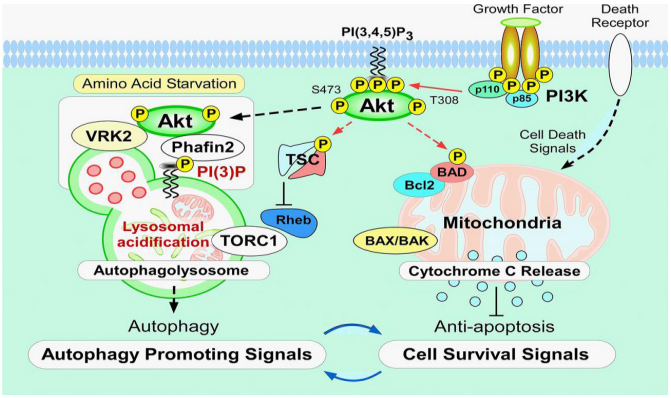

Figure 2: The major mechanisms for cell death have been identified in mammalian cells: apoptosis (type I), autophagic cell death (type II), (Noguchi, M., Hirata, N., Tanaka, T. et al. Autophagy as a modulator of cell death machinery. Cell Death Dis 11, 517 (2020).

The frequencies of gene mutations, deletions or translocations of the P53 gene, in CLL, can be classified as biomarkers of individual proteomic and genomic profile for this type of Leukaemia. MicroRNA expression changes and aberrant methylation patterns in genes that are specifically dysregulated in CLL, including the BCL-2, TCL1, and ZAP-70 genes, have also been found and linked to distinct clinical parameters. Specific chromosomal abnormalities and genetic mutations may serve as diagnostic and prognostic indicators for disease progression and survival. The efficacy of new therapeutics should be tested according to the presence of these molecular lesions in CLL patients.

Main Text

Apoptosis and autoimmunity

The action of apoptosis genes is controlled by the native P53 gene, which by its product, the p53 protein, inhibits the Nk-beta nuclear factor, which is susceptible to protein synthesis in inflammation of autoimmune diseases. Mutations of the P53 gene will lead to insufficient action of the p53 protein and trigger autoimmunity[3].

In this kind, autoimmunity becomes an interface at malignancy by the central element P53 gene. Mutations of the P53 gene will lead to insufficient action of the p53 protein and trigger autoimmunity[4].

Auto-reactive B and T cells, which escaped from natural apoptosis, might represent an additional necessary condition. The link between apoptosis and Tumour Necrosis Factor, TNF, activity shows why abnormal production of TNF plays an important role in several autoimmune diseases and the supplementary mutations in these diseases will drive cells toward cancer[5].

Apoptosis and Malignancy

The most important regulatory mechanisms in the autoimmunity and oncogenesis process are death receptors, DRs), caspases, mitochondria, together with the Bcl-2 family proto-oncogenes of type Bak, Bax and the tumour suppressor gene P53. The treatment with the anti-apoptosis drug, inhibitor of Bcl-2 membrane receptor, Venetoclax, which inhibits overexpressed of anti-apoptosis Bcl-2 receptor, will initiate the mitochondrial apoptosis, **(Figure 3)**.

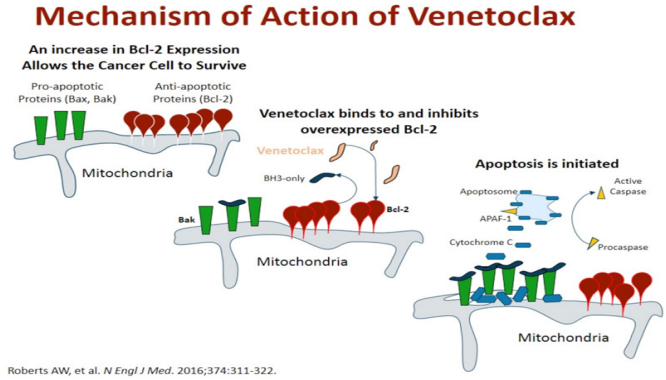

Figure 3: Mitochondria activities leading to apoptosis provide the disruption of transport of membranes cells and the cellular reduction-oxidation potential, (www.Medscape.org, Navigating New Oral Treatment Algorithms in CLL, LLC, New York, accessed in 11/05/2024.).

In the normal health cell, the p53 nuclear protein binds DNA, stimulating another gene, CDKN-IA, to produce a protein called p21 that interacts with a cell division stimulating protein (cdk2)[6].

The expression of the CDKN-IA gene, which encodes protein p21 is tightly controlled by the tumour suppressor protein p53, mediating the cell cycle G1and phase arrest, in response to a variety of stress stimulation. When the p21 protein forms a complex with the cdk2 protein the cell cannot pass through to the next stage of cell division, G1-S. In a normal cell, p53 protein is inactivated by its negative regulator, MDM2. Upon DNA damage or other stresses, various pathways will lead to the dissociation of the p53 and mdm2 complex. Once activated, p53 will induce a cell cycle arrest to allow either repair and survival of the cell or apoptosis to discard the damaged cell[7], **(Figure 4)**.

Methylation at the CDKN-2A gene, (INK4a/ARF locus) can epigenetically silence the expression of the p14-ARF protein, and block the ability of activated oncogenes, to stabilize the p53 response. In experimental models, disrupting the MDM2–p53 interaction restored p53 function and sensitized tumours to chemotherapy or radiotherapy[8].

This strategy could be particularly beneficial in treating cancers that do not contain P53 mutant gene or other specific genetic mutations or deletions (chromosome 11-q, 13-q, 13-14q deletion, deletions 11q22-q23, 7q21 -g23 or trisomy 12); for example, in hematologic malignancies such as multiple myeloma (MM), Chronic Lymphocytic Leukemia, (CLL), with the 17-p chromosomal short arm present and with p-53 genes present, Acute Lymphoblastic Leukemia, (ALL), Acute Myeloid Leukemia and Hodgkin's disease and Non-Hodgkin Lymphoma.

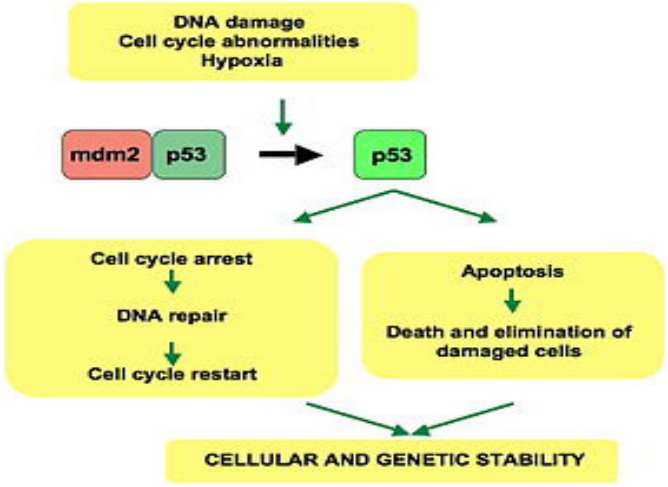

Figure 4: Dissociation of p53 protein and MDM2 protein under stress in a normal cell induces apoptosis.

In the presence of gene P53 mutations, immune treatments with p53 anti-peptide antibodies are being tested. In these tumour types, the induction of p53, using a small-molecule inhibitor of MDM2, Nutlin, can induce apoptosis in malignant cells, **(Figure 5)**[9].

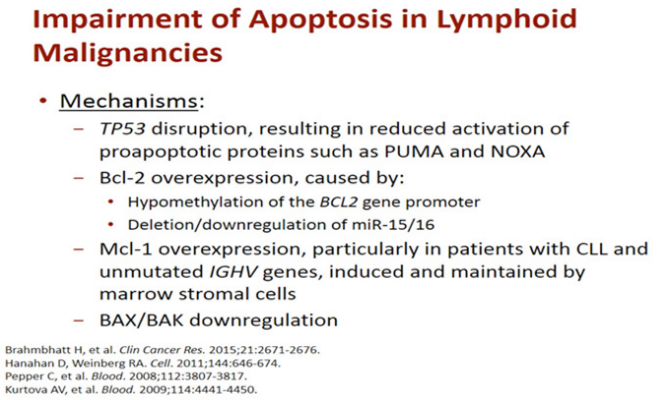

Figure 5: Induction of p53, using a small-molecule inhibitor of MDM2, Nutlin, can induce apoptosis in malignant cells

The p21 protein as a regulator of cell cycle progression from G1 to S phase is controlled by the tumor protein p53. Not surprisingly, there is an increased frequency of amplification of the MDM2 gene in many human cancers as a mechanism for the down-regulation of p53 activity through ubiquitin-dependent proteosome degradation of intra-cytoplasmic p53. A mutant p53 protein no longer binds effectively to DNA, and consequently its activating protein p21 will not be available to act as the "stop signal" for uncontrolled cell division, **(Figure 6)**.

Antibodies specific for total p53 protein and for p53 reactive, phosphorylated at three different sites within the activation domain, were used in parallel analyses in different malignant diseases. The change of Serine-15 amino-acid, in p53 protein, to alanine, results in partial failure of p53 protein to inhibit cell cycle progression and drive toward cancer. In this context, the nuclear p53 protein was shown to protect the cell from a malignant process, and only cytoplasmic p53 protein, by its isoforms, phosphorylated in multi-sites, into modified

cytoplasmic medium, by high concentration of anaerobic ATP develop cancer diseases, **(Figure 7)**.

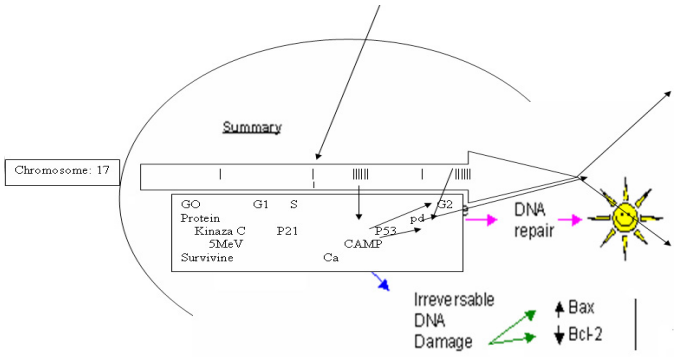

Figure 6: p21 protein as a regulator of cell cycle progression from G1 to S phase is controlled by the tumor protein p53. [Udriștioiu A, Florescu C, Popescu AM, Cojocaru M. High concentration of anaerobic ATP implicated in aborted apoptosis from CLL, Lab. Med. 41; 2010: 203–8].

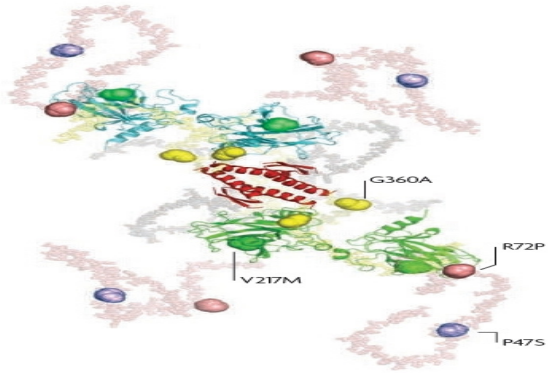

Figure 7: Three-dimensional structure of isoform p53 protein in tetrameric form.

In most tumours, the p53 protein is inactivated by mutations in the P53 gene that lead to the production of a p53 protein with increased stability in B-cell lymphocytes. This leads to the identification and quantification of the p53 protein by various molecular techniques, immunohistochemistry, PCR, SNP or ELISA, of the p53 protein positive with the mutant P53 gene, unlike normal B-cells, which contains the wild-type p53 protein, which contains a small amount of p53 protein, with a very short half-life[10].

Expression of variable immunoglobulin heavy chain (IGHV) genes, ZAP-70 and CD38 proteins, and the occurrence of chromosomal abnormalities such as 17p deletions have been associated with a poor prognosis in CLL. In addition, mutations in tumour suppressor genes, such as the P53 gene and ATM, have been associated with refractory to conventional chemotherapeutic agents[11].

MicroRNA expression changes and aberrant methylation patterns in genes that are specifically dysregulated in CLL, including the BCL-2, TCL1, and ZAP-70 genes, have also been reported in the literature, linked to clinical parameters that distinguish relapses from relapses of CLL stages.

Specific chromosomal abnormalities and genetic mutations may serve as diagnostic and prognostic indicators for disease progression and survival of CLL patients. The efficacy of new therapeutics should be tested according to the presence of these molecular lesions in CLL patients[12].

Frequent alterations in the P53 gene have been found in more than 75% of CLL cases. The MDM2 overexpression involves the repression of a large number of p-53-dependent genes and mRNAs, including microRNA-34a. Alterations in microRNA expression and aberrant methylation patterns in genes that are specifically dysregulated in CLL, including the BCL-2, TCL1, and ZAP-70 genes, have also been found and linked to distinct clinical parameters. Since this microRNA is involved in the induction of apoptosis depression and cell cycle arrest, a more aggressive disease course may be correlated with overexpression of microRNA-34[13].

A large cohort study of primary CLL examined samples from more than 100 patients for response to MDM2 inhibition and found a direct correlation between wild-type P53 status and MDM2 inhibitor, Nutlin-3 and MI-219, induced cytotoxicity across various CLL subtypes. This response was not predicted by other biomarkers used clinically in CLL, including expression of ZAP70, expression of CD38 receptor on malignant B cells, un-mutated immunoglobulin variable genes, IGHV and mono-allelic ATM gene loss[14].

A large number of patients with cancer produce p53-reactive phosphorylated T cells and more than 40% of patients with breast cancer have p53-reactive CD-4 and CD-8 T cells in their peripheral blood. These responses occur most frequently in patients with high p53 protein expression in their tumours. The current study showed that the level of p21 is strongly correlated with the activity of Mammalian Target Rapamycin, mTOR. Activated mitogen Protein Kinase, (AMPK), an inductor factors of acetylation, methylation and phosphorylation of sites p53 protein, activates protein p53 protein in DNA damage, **(Figure 8)**.

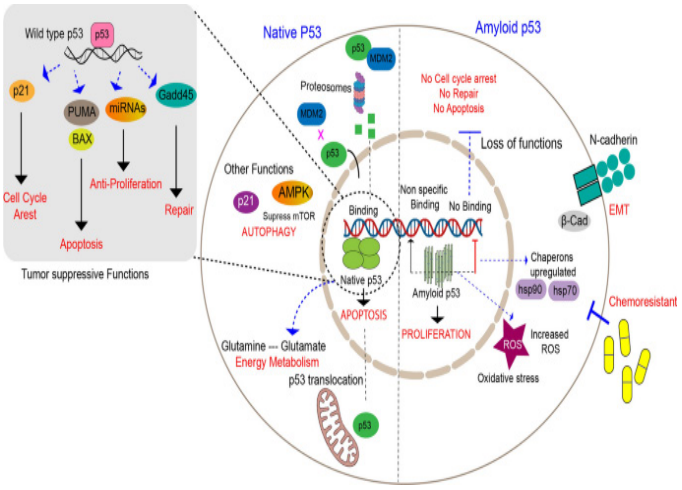

Figure 8: Activated mitogen Protein Kinase, (AMPK) and p21 protein suppress mTOR complex in autophagy process drive to apoptosis, (www.Medscape.org, accessed on 03/03/2025).

Intracellular ATP levels are a core determinant in the development of acquired cross-drug resistance of human cancer cells that carry out different genetic backgrounds. Drug-resistant cells were characterized by defective mitochondrial ATP production, elevated aerobic glycolysis, higher absolute levels of anaerobic intracellular ATP and enhanced HIF-1α-mediated signal. When the cellular concentrations of ATP are high, typically >5 m-Mols it was thought that a high concentration of drug would be needed for efficacy with ATP-competitive inhibitors, bringing potential toxicity problems[15].

The study was published in the February 2, 2016, online edition of the Journal Nature Communication, (www.cnio.es). By the Warburg effect, glucose maintains the stability mutant P53 gene and promotes cancer cells. Most researches seem to indicate that, in line with its role as a tumour suppressor p53 is able to fall glycolysis[16].

The mTORc2/Akt complex controls mitochondrial metabolism and physiology, through the phosphorylation of the glycolytic enzyme hexokinase 2, thus promoting cancer cell's aerobic glycolysis (Warburg effect) and preventing mitochondrial apoptosis[17].

Also, the Aurora kinases, enzymes A and B, play critical roles in regulating spindle assembly, chromosome segregation, and cytokinesis to ensure faithful segregation of chromosomes during the mitotic cell division cycle. Aberrant expression of Aurora kinases, on the other hand, causes defects in mitotic spindle assembly, checkpoint response activation, and chromosome segregation leading to chromosomal instability.

In contrast to the effect of Aurora-A phosphorylation on p53 activity and stability, Aurora-B phosphorylation of p53 at serine-269 and threonine- 284 inhibit p-53 transactivation activity, whereas phosphorylation at serine-183, threonine-211, and serine-215 accelerates the degradation of p53 through protease enzyme [MDM2][18].

Autoimmune phenomena are frequently observed in patients with CLL and are mainly attributable to underlying dysfunctions of the immune system. Also, autoimmune cytopenia, (AIC), affect 4-7% of patients with CLL and mainly consist of autoimmune hemolytic anaemia and immune thrombocytopenia.

The definition of autoimmune hemolytic anaemia, (AIHA), considers the presence of all the following criteria: Haemoglobin, (Hb), levels lower than or equal to 11 g/dL, in the absence of any cytotoxic treatment in the preceding month or other etiology identified, evidence of an underlying autoimmune mechanism, such as a positive direct antiglobulin test, (DAT), for either immune-globulin IgG or complement C3 or the presence of cold agglutinin and presence of one or more laboratory marker of hemolysis as the high reticulocyte count, low serum haptoglobin levels, increased serum lactate dehydrogenase, (LDH), and indirect bilirubin levels[19].

Whereas the association of CLL with autoimmune cytopenia, particularly autoimmune haemolytic anaemia and immune thrombocytopenia, is well established, there is no proof of an increased risk of non-hemic autoimmune disorders in CLL. The mechanisms leading to autoimmune cytopenia in CLL are complex and involve interactions between the malignant B-CLL cells, abnormally functioning T cells, the microenvironment, and the immune system. Patients showing anaemia, associated with the presence of anti-erythrocyte autoantibody (Ae-Ab), were considered as CLL with AHA. The Ae-Ab complex and the Complement bound to the red cell membrane are detected by the direct antiglobulin test, (DAT), using a broad-spectrum antiserum[20].

The autoimmune hemolytic anemia (AIHA) appearing in 5% to 10% of the patients with CLL, and autoimmune immune thrombocytopenia (ITP) in 2% to 5% of patients with CLL. AIC may be diagnosed before, at presentation, or at any point during the course of CLL. It may also be observed in either untreated or treated patients. Also, AIC tends to appear in patients with high-risk CLL (ex, unmutated immunoglobulin heavy chain variable region gene, [IGHV], 17p and 11q deletion)[21].

In the studies conducted from years 2025, highly effective treatments of CLL, combining fludarabine with other agents (ie, cyclophosphamide, [FC], FC + rituximab, [FCR]), were associated with a low proportion of AIHA then another previous standard chemotherapy along years. Taken together, these results convincingly suggest that rather than treatment it is the lack of response to it that conveys a higher risk of AIC. Also, two retrospective studies addressed the prevalence of AIC in subjects with CLL-treated ibrutinib and/or idelalisib, as well as their efficacy in AIC, if present[22,23].

Conclusion

Presented researches are impact on the clinical management of patients and require an attitude adjustment therapeutic adequate in a personalized medicine. Personalized treatments will be applied by combining diagnostic tools, knowledge databases and therapeutic drugs.

Abbreviations

AMPK 5'-AMP -activated protein kinase

HIF-1α, hypoxia-inducible factor-1α

MAP- kinase interacting kinase;

MAPK- mitogen-activated protein kinases;

MEK, -MAPK/ERK kinase;

mTOR-mammalian target of rapamycin

MDM2-mouse double minute 2 homolog

PI3K-phosphatidyl inositol-4,5-bisphosphate-3-Kinase

TGF-α, transforming growth factor α

VEGF-vascular endothelial growth factor

Statements relating to ethics and integrity policies

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Permission to Reproduce Material from Other Sources

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