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Cholesterol and Triglycerides Metabolism Disorder in Malignant Hemopathies

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1. Introduction

The aim of this chapter is to achieve a synthesis of the major studies existing in the literature on correlations between lipid metabolism and malignant hemopathies. We will expose the fundamental research data and their impact on clinical treatment. The purpose of this review is to help the clinicians to understand better the pathological disorders of the lipid metabolism and use the existing therapeutic arsenal to improve the treatment outcomes. The research and the recognition of the presence of dyslipidemia is useful, as well as monitoring them during oncological therapy. The treatment of dyslipidemia may not be only an option when a patient with malignant hemopathy has acquired multidrug resistance. It can contribute to reversing this resistance, but it can also have adverse effects that must be recognized, followed and treated.

There are numerous studies in literature, but the connection between blood levels of various lipid fractions and hematologic malignancies is still unknown (Cvetkovic et al., 2009). Various epidemiological studies have found that between blood lipids and various neoplastic diseases there are correlations, thus the question is whether in the pathogenesis of cancer are not involved various lipid disorders (Moschovi M et al., 2004). At the same time it is believed that in patients with metabolic syndrome (MS), blood lipid levels may have correlations with the risk of cancer (Ulmer H et al., 2009).

2. The lipid profile evolution under cancer treatment

Cvetkovic & al. studied 47 patients with malignant non-Hodgkin's lymphoma (NHL) and found that before the treatment, compared with patients in the control group, blood levels of phospholipids, cholesterol (CH) and high density lipoprotein-cholesterol (HDL-cholesterol) had significantly lower values. After chemotherapy (3 or 6 cycles) the blood lipid levels reached even lower values in patients where the disease progressed, as opposed to those who achieved complete remission or whose disease was stationary, cases in which lipids increased progressively. (Cvetkovic et al., 2009).

In an other study conducted in Poland on the lipid levels of 238 patients with different hematological malignant diseases Kuliszkievicz-Janus M et al. found that HDL-cholesterol values were significantly different from those of patients in the control group when the disease was in active phase, but in the remission phase the difference was statistically significant only in patients with NHL and acute leukemia (Kuliszkievicz-Janus et al., 2008).

In a health investigation conducted on 156,153 subjects, with 5079 incident cancers in men and 4738 cancers in women, and a mean of 10.6 years of survey, there was an inverse association between serum triglyceride (TG) levels and NHL (2). But in the study conducted by Kuliszkiewicz-Janus M et al., the TG value increased in the active disease period in all the hematological malignancies besides NHL (Kuliszkiewicz-Janus et al., 2008).

Mihăilă R and al. made a cross-sectional research on all the patients with chronic lymphocytic leukemia (CLL) existing in a county department of hematology and a group of volunteer subjects from the medical staff with no malignant pathology. They found an augmentation of TG values in the patients with CLL ($p < 0.00001$), an argument for a possible link between the MS and chronic lymphoproliferations. Hypercholesterolemia present in the patients with CLL from the above study may have consequences regarding the multiple drug resistance, subject to further future study. (Mihăilă et al., 2010)

Nearly all the children with ALL when diagnosed and during chemotherapy revealed a predictable model of serum dyslipidemia that consisted of very low levels of HDL-cholesterol, and elevated TG, and low-density lipoprotein cholesterol (LDL-cholesterol), that regained normal values during the remission period (Moschovi et al., 2004).

In patients with secondary hemophagocytic syndrome an augmentation of TG was observed when diagnosed or during the disease period and TG values decreased when the disease improved under treatment (Okamoto et al., 2009). In patients with aggressive T cell lymphoma, fasting TG level was higher in those with hemophagocytic syndrome group than in the patients who had no hemophagocytic syndrome (Tong et al., 2008).

3. The consequences of treatments with antineoplastic drugs

In children with acute lymphoblastic leukemia (ALL), treated with asparaginase dyslipidemia was frequently observed (Cohen et al., 2010).

A child heterozygote for apolipoprotein E 3/4 and with ALL who received pegasparaginase, presented an important augmentation of serum TG value, which normalized after continuous insulin infusion (Lawson et al., 2011). Another patient with a heterozygote type of familial lipoprotein lipase defect syndrome developed an important increase of serum TG value that was treated by three plasma exchanges with frozen plasma (Nakagawa et al., 2008).

An adult patient with ALL also had an acute pancreatitis because of an important hypertriglyceridemia that appeared after asparaginase administration (Kfoury-Baz et al., 2008), as well as a 10 years old boy who had been previously treated with asparaginase and corticosteroids (Ridola et al., 2008), both successfully treated by plasmapheresis sessions (Kfoury-Baz et al., 2008; Ridola et al., 2008).

In a group of children and adolescent patients recently diagnosed with ALL during treatment a progressive increase of serum CH values to 274 ± 124 mg/dl was observed. In this group of patients the average value of TG during treatment was 459 ± 526 mg/dl. Two patients had hypertriglyceridemia-related complications: a thrombosis of sagittal sinus and an infarct of the left frontal lobe. The observed dyslipidemia disappeared in all children after the asparaginase administration (Cohen et al., 2010).

A prospective study assessed the lipid levels in children with ALL. At diagnosis, there was a significantly low level of total CH and HDL-cholesterol and at the same time a high level of TG. The patients were treated with the ALLIC 2002 protocol (including L-asparaginase), during which the values of total CH and HDL-cholesterol augmented, but they still

remained lower than for the control group. The main serum TG level was significantly higher as compared to that of witnesses (Zalewska-Szewczyk et al., 2008).

A retrospective analysis showed that imatinib mesylate, used for the treatment of patients with chronic myeloid leukemia, led to a diminishing of serum CH and TG values (Franceschino et al., 2008). In a Romanian patient with chronic myeloid leukemia who received usual-dose of imatinib mesylate, a rapid and sustained normalization of serum CH, TG, low- and high-density lipoproteins and glucose values was found (Gologan et al., 2009). In some types of leukemia it was found that Kit receptor tyrosine kinase is overexpressed in a pathological manner, also that CH depletion was able to prevent Kit-mediated activation of the phosphatidylinositol 3-kinase downstream target Akt, which inhibits cell proliferation (Jahn et al., 2007).

The treatment of cutaneous lymphomas with T cells using bexarotene can produce a serum TG augmentation, as in the three cases reported. The treatment with fenofibrate is recommended, but if adverse effects occur or a statin is needed to reduce hypertriglyceridemia, omega-3 fatty acids may be a therapeutic solution during the bexarotene administration. (Musolino et al., 2009)

4. Is the metabolic syndrome a risk factor for some malignant hemopathies?

The main risk factors for excess weight and obesity are high caloric diet and sedentary lifestyle. A study conducted in a county hospital in Transylvania examined the presence of MS in all 56 patients with NHL existing in its records and a control group of 64 consecutive patients with non-cancerous diseases in the same hospital (control group). Patients with NHL had significantly more frequently arterial hypertension, significantly higher body mass index values, and a significantly higher number of components of the MS as compared to those of the control group. This observation advocates the idea that excess weight may be a risk factor for this type of neoplasia. (Mihăilă et al., 2009)

In a group of 170 non-Hispanic white pediatric cancer survivors, among males, body adiposity was more important in survivors than in witnesses, as was trunk fat. The survivors had higher values of CH, TG, LDL-cholesterol than the witnesses, and the first watched TV more hours than controls (Miller TL et al., 2010). It was observed that the young survivors of ALL, disease which they had in their childhood, especially those who received cranial radiotherapy, are likely to develop hyperlipidemia, insulin resistance, obesity, arterial hypertension and even MS soon after the treatment (Trimis et al., 2007).

After an average period of 37 months after the end of type ALL-BFM 90 chemotherapy protocol, out of 52 patients almost half were overweight, nearly 6% - obese, more than half had at least one risk factor for MS, and about 6% had MS (Kourti et al., 2005).

It was found that the consequences of treatment performed for ALL during childhood may become manifest when subjects reach adulthood. Cranial irradiation favors more the appearance of MS: 60% of those who had been so treated had at least two of the five components of MS when they become adults, and only 20% of those who had not been irradiated. The pathogenetic mechanism that explains the metabolic effects of cranial irradiation implies growth hormone (GH) deficiency, lower level of insulin-like growth factor 1, fasting hyperinsulinemia, abdominal obesity and hyperlipidemia, especially in women (Gurney et al., 2006). In another study, ALL survivors who received cranial irradiation developed more frequently MS than those nonirradiated (23% towards 7%), probably because of higher prevalence of excess weight and arterial hypertension (van Waas et al., 2010).

In a study conducted on a group of 184 adults who had ALL in their childhood, the overall prevalence of MS has been even higher - 9.2%. Peripheral stem cell allografts after total body irradiation favored the occurrence of hypertriglyceridemia, low HDL-cholesterol and increased fasting glucose level (Oudin et al., 2011).

In Sweden a group of adults was analysed; they survived after ALL during childhood and were submitted to radio-and chemotherapy. Those who received treatment for 5 years with GH compared with those not treated so for 8 years, showed significant changes in HDL-cholesterol, glucose and apolipoprotein B / apolipoprotein A1 ratio, and MS was significantly less frequent. (Follin et al., 2010)

Another study conducted in Sweden on adults who had childhood leukemia, found an augmentation of total body fat, especially of trunk adiposity and an evolution towards an unfavorable lipid spectrum. These observations were correlated with low levels of endocrine secretion of GH, a consequence of previous cranial irradiation. (Jarfelt et al., 2005)

An interesting combination of diseases was described in a 54 years old woman: after being diagnosed with chronic neutrophilic leukemia a liver biopsy was made. The histopathological diagnosis was of nonalcoholic steatohepatitis (NASH) with neutrophilic infiltrate. The authors consider that the leukemia cells that infiltrated the liver contributed to the emergence of NASH. The administration of cytosine arabinoside contributed to a significant decrease in fat degeneration. (Yoshida et al., 2004)

There are few studies on the metabolism of chylomicrons in patients with cancer. The study of a group of patients with Hodgkin and nonHodgkin lymphoma, as compared to a healthy control group, led to the observation that after an intravenous administration of a chylomicron-like emulsion, the levels of CH, TG and VLDL were significantly higher in patients with lymphoma because of the profound disturbance of the chylomicrons lipolysis and their removal deficit. (Gonçalves et al., 2003)

A very interesting observation was achieved in a line of promyelocytic leukemia NB4 cells: the administration of peroxisome proliferator-activated receptor gamma ligands was able not only to induce differentiation but also to favor lipogenesis in NB4 cells. This fact suggests a close link between differentiation and lipogenesis process in human myeloid cells thus stimulated. (Yasugi et al., 2006).

5. Cholesterol metabolism disorder

It is known that cell membranes contain lipid rafts, belonging to CH-rich microdomains. These components of the cell membrane are involved in intracellular signal transduction processes mediated by the receptor and in the self-renewal of ES cells. (Lee et al., 2010) The administration of methyl-beta-cyclodextrin, that is a CH-sequestering agent useful for the lipid raft destruction, is able to restore the activity of large conductance background K(+) channels. This favors the activation by stretch. (Nam et al., 2007) The depletion of CH from the cell membranes leads to lipid rafts destruction, that are responsible for blocking the translocation of leukemia inhibitory factor receptor and gp 130 (Port et al., 2007).

A group of Russian researchers studied the role of membrane CH in a line of human leukaemia K562 cells regarding the regulation of mechanosensitive cation channels activated by stretch. They consider that the above-mentioned suppression of this channel activation in leukemia cell line by methyl-beta-cyclodextrin is produced by F-actin rearrangement due to lipid raft destruction. (Morachevskaya et al., 2007)

In the regulation of lipid and CH metabolism liver X receptors are also involved, they are nuclear receptors. They can modulate the proliferation and survival of both normal and malignant B and T lymphocytes. (Geyeregger et al., 2009)

The correlation between increasing CH in lipid domains and the possible cancerous cell transformation is very interesting (Ajith et al., 2008). It is believed that CH is important for cell proliferation, because low serum CH values may be the result of high cellular CH need of cancerous cells. Low serum CH values correlate with elevated levels of CH in lymphocytes. Evidence of low levels of CH in the culture medium is due to the development of lymphoma cells, which would consume more CH for their own proliferation. The experimental administration of mevastatin in vitro, which inhibits CH synthesis, did not determine a significant variation of the concentration of CH in the culture medium, while cell growth diminished. (Pugliese et al., 2010)

Low serum CH levels are also frequently found in acute leukemia patients. These patients have significantly lower serum values of CH, HDL-cholesterol, and LDL-cholesterol. A possible explanation for the low levels of HDL-cholesterol in the patients with acute leukemia could be an increased expression of a possible selective site for HDL-cholesteryl ester. (Gonçalves et al., 2005)

Malignant, proliferative cells have an intense metabolism of CH, while decreased intake of CH is responsible for decreasing cell proliferation. In a human line of promyelocytic HL-60 cells, an inhibition of cell cycle progression from G2 phase can be obtained by an enzymatic inhibition of CH synthesis at a stage before 7-dehydrocholesterol production. Drugs such as zaragozic acid or SKF 104976 can induce the expression of antigen 11c, a cluster of differentiation. These products have a comparable action to all-trans retinoic acid, which induces monocyte differentiation. (Sánchez-Martín et al., 2007)

Chronic lymphocytic leukemia (CLL) is a heterogenous malignant hemopathy. In these patients, in the presence of UM-IGHV, which is a negative prognostic factor, there are increased levels of CH and lactate and low levels of glycerol and 3-hydroxybutyrate. (MacIntyre et al., 2010)

CD5 antigen is responsible for CH synthesis and even for adipogenesis. It is known that malignant cells from CLL are undergoing a process of continuous stimulation due to CD5 activation and cell survival. (Gary-Gouy et al., 2007) A continuous activation of an antiapoptotic pathway explains the CLL cells survival. Apolipoprotein E4-very low density lipoproteins is responsible for the high level of apoptosis in CLL cells. Lipoprotein lipase is the enzyme that metabolizes very low density lipoproteins to low-density lipoprotein. It was observed that an increase of lipoprotein lipase mRNA levels is present in CLL patients with shorter survival. (Weinberg et al., 2008)

CH synthesis is also increased in patients with T-ALL who are glucocorticoid resistant (Beesley et al., 2009).

The growth of a promyelocytic leukemia cell line – HL-60 can be experimentally suppressed by sodium cholesteryl sulfate, cholesteryl bromide, and cholesteryl-5alpha. The first two are responsible for the cell arrest in S and G2/M phases, and the last product – in the G2/M phase. (Ishimaru et al., 2008)

It was found that in xenotransplanted severely combined immunodeficient mice the most abundant bone marrow CH amounts are located in leukemia-rich sites. In vitro, in leukemic cells CH is able to stimulate FLT-1 expression and VEGF production. Human leukemic cells from patients with AML are significantly richer in CH than normal cells and this CH augmentation represents a marker of aggressive evolution. (Casalou et al., 2011)

6. Experimental and clinical observations on cholesterol metabolism disorder

ABCA1 and ApoA-I are responsible for the efflux of CH in human monocyte leukemia cell line derived foam cells. This decrease of the concentration of CH can be enhanced by administration of rosiglitazone. (Lü et al., 2010) Animals fed on alternate days have showed lower incidence of lymphomas, after tumor inoculation have had higher survival, and some types of cells have proliferated more slowly. It seems that this diet in humans would favor increased levels of HDL-cholesterol and lower those of triacylglycerol. (Varady et al., 2007) It was found that ether phospholipid edelfosine is able to accumulate and selectively destroy mantle cell lymphoma and CLL cells, underlining the importance of the action on lipid rafts and Fas/CD95 for the therapy of these lymphoproliferations. CH depletion is involved in lipid raft disruption and in the diminishing of drug captation. (Mollinedo et al., 2010) Some clinical observations on the presence of dyslipidemia in patients with malignant hemopathies are presented in Table 1.

Author	Disease	Dyslipidemia
Inamoto et al., 2005	ALL + cholestasis from graft versus host disease	hypercholesterolemia
Lim et al., 2007	NHL	serum HDL-cholesterol decrease
Gokhale et al., 2007	NHL	serum total CH level was significantly higher in patients who completed the treatment for NHL than in those who completed ALL therapy
Garg et al., 2011	intravascular large B cell lymphoma	low serum levels of HDL-cholesterol
Helman et al., 2011	MALT + obesity	hypercholesterolemia

MALT = mucosa-associated lymphoid tissue lymphoma

Table 1. Examples of dyslipidemia in patients with malignant hemopathies.

7. The cholesterol and the treatment with anti-CD20 monoclonal antibodies

It has been noted that the loss of CH is responsible for the decrease in the number of sites that can fix some monoclonal antibodies, including CD20. CH depletion or Shiga-like toxin binding have been causes of disruption of CD20 localization, but not of CD77 in lipid rafts. (Jarvis et al., 2007) DXL625 is an anti-CD20 monoclonal antibody, capable of causing independently in vitro apoptosis of a lymphoma B cells line. This apoptosis is inhibited by the loss of membrane CH or of chelation of extracellular calcium, fact that underlines the role of lipid raft and calcium in this process. (Bingaman et al., 2010) Many lymphoproliferations with B cells have indication of treatment with rituximab, an anti-CD20 antibody. The inhibitor therapeutic effect of rituximab occurs at the same time as the decrease of CH deposits from lipid rafts, with decreased B-cell receptor relocation to lipid rafts structures, and with the disruption of the expression of BCR immunoglobulin, lowering it. (Kheirallah et al., 2010)

The first monoclonal antibody that was approved for the treatment of B-cell lymphoproliferative malignancies was rituxan, a chimeric monoclonal anti-CD20 antibody. It has been observed that the monoclonal antibody attachment to CD20 produces a redistribution of these antigens to lipid rafts, which are specialized membrane microdomains. If rituxan is not used, the CD20 antigen affinity to lipid rafts is small. Intracellular calcium entry and apoptosis have been completely eliminated experimentally by extracting CH, which has led to the destruction of the integrity of lipid raft structures and to the dissociation of CD20 antigen from a fraction that is resistant to Triton X-100. From this it results that for the activation of caspase induced by CD20- lipid rafts appear to have an essential role. (Janas et al., 2005)

In multidrug resistance two populations of P-glycoprotein (P-gp) are involved. One is located in the membrane regions that are resistant to detergent; it has optimal P-gp ATPase activity; the verapamil can activate it and the orthovanadate can inhibit it almost entirely. The other population is located in another part of the membrane; it has less activity than P-gp ATPase of the first population; the verapamil can inhibit it, and its sensitivity to the orthovanadate is less. The first population of Pgp is surrounded by deposits of CH that may have the role to stimulate the P-gp ATPase activity, but the CH near the second population of Pgp does not seem to have such a role. (Barakat et al., 2005)

Rituximab induced apoptosis may be diminished by depletion of membrane deposits of CH, which does not allow the association to the detergent-insoluble lipid rafts of the antigen hypercrosslinked CD20. Under the action of rituximab, the antibody-bound CD20, found in lipid rafts in a high-affinity structure, activates src family kinases, interfering with the signal-transmission mechanism, which it inhibits. (Unruh et al., 2005)

Besides their CH-lowering effects, statins have pleiotropic effects, including the antileukemic ones observed in vitro and in vivo (Sassano et al., 2009), but they disrupt the binding (Winiarska et al., 2008) and the antitumour activity of rituximab (Ennishi et al., 2010), as a consequence of the changing of the antigen CD20 conformation (Ennishi et al., 2010; Winiarska et al., 2008). Statins interfere with the detection of CD20 as well as the antilymphomatous function of the rituximab (Winiarska et al., 2008). But in a study that analyzed the progression-free survival in 3 years and overall survival in a group of patients with diffuse large B-cell lymphoma, including some patients who were taking statins, it was found that there were no statistically significant differences, fact that advocates the idea that statins used in clinical treatment do not alter the prognosis of patients with diffuse large B-cell lymphoma under R-CHOP treatment. (Ennishi et al., 2010)

8. Statins as adjuvant treatment in malignant hemopathies

After chemotherapy, the blasts of acute myeloid leukemia (AML) respond by increasing cellular content of CH, which increases resistance to treatment. (Kornblau et al., 2007) Statins are pharmacologic inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) - the regulatory enzyme of CH synthesis (Nonaka et al., 2009; Sassano et al., 2007). In vitro, they block HMG-CoA reductase and by this they contribute to restore sensitivity to chemotherapy. (Kornblau et al., 2007) HMG-CoA regulates not only the synthesis of CH but also that of the higher isoprenoids, as geranylgeranyl pyrophosphate (Fuchs et al., 2008). By the inhibition of the prenylation processes, in vitro, statins reduce cellular proliferation and stimulate apoptosis of cancerous cells (Nonaka et al., 2009; Sassano et al., 2007). It was found that simvastatin inhibits geranylgeranylation processes of small

GTPases Rab5B and Rac1 in certain leukemic cells (for example, adult T-cell leukemia). (Nonaka et al., 2009)

The excessive proliferation inhibition induced by simvastatin results from the induction of apoptosis, cell cycle arrest in phase G2 / M, and accumulation of p21 protein. Simvastatin is able to remove resistance to apoptosis that occurs during treatment with bortezomib, by reducing geranylgeranyl pyrophosphate synthesis and cell survival mechanism dependant on this. (Fuchs et al., 2008) In IgM secreting cell lines and cells from Waldenstrom macroglobulinaemia, simvastatin showed antiproliferative and cytotoxic effects and stimulated the apoptosis. Simvastatin had a synergistic effect with bortezomib, dexamethasone and fludarabine by augmenting their cytotoxicity. (Moreau et al., 2008).

A group of 23 patients with lymphoproliferative diseases, for which statins had not been contraindicated, was treated for 3 days with simvastatin at a dose of 120 mg/day. Serum CH level and that of total lipids decreased significantly ($p < 0.001$ and, respectively, $p = 0.016$). Serum ALT decreased insignificantly, while that of AST increased, the growth was close to the statistical significance limit, but was not higher than the upper normal level. Flowcytometric dosage of annexine V showed that simvastatin induced early and late apoptosis increase ($p = 0.007$, respectively, $p = 0.003$). By its effect on apoptosis, simvastatin could be an adjuvant treatment for patients with lymphoproliferative disorders. (Mihăilă et al., 2009)

By their CH-lowering effect, statins are promising drugs for the treatment of lymphomas (63 Winiarska et al., 2008). A female patient suffering from NHL with large B-cells whose primary location was the mammary gland had hypercholesterolemia, hypertriglyceridemia and was hypertensive. During the treatment with R-CHOP and radiotherapy that followed (30 Gy), she received lovastatin (20 mg/day) and verapamil. After the first 30 days of treatment, both CH and TG were normalized, and after the whole treatment, the patient has been in complete remission that persists today. (Mihăilă et al., 2008) Lovastatin was administered to the patient not only because she was dyslipidemic, but also because the literature claims that the drug is useful in malignant lymphomas, leukemias and multiple myeloma by its pleiotropic effects. In 1998 the first article about a farnesyltransferase inhibitor (L-744, 832) was published, inhibitor that proved to be effective in mice with mammary carcinomas and lymphomas (Mangues et al., 1998). Lovastatin acts by inhibition of geranylgeranylation, followed by reduction of intracellular signaling mechanisms, which results in reduction of time and dose-dependency of the viability of lymphoma cells in vitro. This is the result of apoptosis stimulation as well as of the decrease of lymphoma cells proliferation, the latter by induction of G1 arrest in cell cycle (van de Donk et al., 2003).

In a rat lymphoma model lovastatin administration during radiotherapy led to cell cycle arrest in different phases, which justified the continuation of the treatment with this drug in the female patient during radiotherapy; the experimental model mentioned, the combination of lovastatin with radiotherapy resulted in a synergistic action (Rozados et al., 2005, as cited in Mihăilă et al., 2008). Lovastatin administration did not preclude the response to polychemotherapy that included rituximab. In fact, although it is only one case, the experimental findings do not always overlap with clinical outcomes. The authors consider that the combination of lovastatin with verapamil favored the response to anticancer treatment and prevented the possible multidrug resistance (Mihăilă et al., 2008). The combination of lovastatin + R-CHOP did not lead to adverse effects. Six years after the end of therapy, the patient is still in complete remission.

In a cell line of acute promyelocytic leukemia (NB4) atorvastatin and fluvastatin showed to be potent stimulators of cell differentiation and apoptosis (Sassano et al., 2007). When to the treatment with idarubicin and high-dose cytarabine of patients with AML pravastatin was added, CR / CRp was observed in 11 of 15 new patients, out of which 8 of 10 had unfavorable cytogenetics, and 9 of 22 patients who received rescue medication that pravastatin did not influence the length of neutropenia, of thrombocytopenia or of the toxicity of chemotherapy. (Kornblau et al., 2007)

Statins are active also in acute promyelocytic leukemia cells, where they augment the antileukemic response that depends on all-trans retinoic acid (ATRA). The c-Jun NH₂-terminal kinase pathway is required for leukemic cells differentiation induced by statins. Statins also intervene in modulating ATRA-dependent transcription. This was revealed by the selective expression of a large number of genes (400) when atorvastatin was administered together with ATRA. (Sassano et al., 2009) This drug combination could be a solution for reversing the ATRA-resistance of leukemic cells (Sassano et al., 2007).

Unlike the subgroup of normal and AML cells CD34 (-), the CD34 (+) is more sensitive to lovastatin. Both populations of cells were strongly inhibited when lovastatin was added to chemotherapy. Leukemic cell samples from different patients with AML had heterogeneous sensitivity to lovastatin. Fifty percent of the patients with unfavorable treatment response had cytogenetic examination with poor prognosis and significantly more blasts in the peripheral blood. (de Jonge-Peeters et al., 2009)

It was observed that high expression of CXCR4 correlates with a shorter survival time of patients with AML. In some models of cancer hypoxia it leads to the increase of CXCR4. On the other hand, increased pO₂ causes depletion of CH, which alters lipid rafts and leads to structural changes, which result in increased rejection of CXCR4 microparticles. (Fiegl et al., 2009) Atorvastatin administered in doses of 16 mg/kg body wt showed to be effective in the inhibition of ascites tumor growth and induced apoptosis of a cell line of Daltons' Lymphoma Ascites that was transplanted into mice (Ajith et al., 2008).

In vitro, simvastatin induced apoptosis of CLL cells, found in short term culture and contributed to lower BCL-2/BAX report; it was found that its effect of apoptosis induction is tumor-specific and does not affect normal lymphocytes. The association of simvastatin with fludarabine or cladribine synergistically induces DNA damages, and these lead to apoptosis. The proportion of cells found in apoptosis induced by simvastatin +/- chemotherapy was not correlated with the expression of negative prognostic markers of the disease (ZAP-70 and CD38) or its stage in the RAI classification. (Podhorecka et al., 2010)

The interaction of adhesion molecules, with fundamental role in cellular interaction processes, including those concerning EBV-transformed B cells is blocked by some statins. These drugs also inhibit intracellular activation of NF-kappaB and contribute to the emergence of transformed B-cell apoptosis. In mice with severe combined immune deficiency, simvastatin caused delayed emergence of the lymphomas induced by EBV. (Cohen et al., 2005)

Both the simvastatin and the tipifarnib have cytotoxic effect on AML cell lines and their associated administration has a synergistic effect. This combination administered to CD34(+) AML cells resulted in the increase of the inhibitory effect only on normally responsive AML cells; however, the combination administered to CD34(-) AML cells had augmented inhibitory effect in all cells. (van der Weide et al., 2009)

It was observed that statins are able to decrease the expression of BCL-2, an antiapoptotic molecule, favoring the appearance of apoptosis of CD4(+) CD28(null) T cells - a T aggressive

and long-lasting lymphocyte subpopulation, which can infiltrate the atheromatous plaques, contributing to their destabilization, which facilitates the installation of major coronary accidents. (Link et al., 2011)

9. ABC transporters and cholesterol homeostasis

In many neoplastic diseases, increased expression of proteins on which depends the multidrug resistance correlates with the presence of refractory disease. A small proportion of AML leukemia cells is responsible for the tumor proliferation and expansion. These are leukemic stem cells, primitive cells, which are frequently in a quiescent state. When they leave the quiescent state and progress along the cell cycle, these cells are characterized by the ability of self-renewal and express some ATP-binding cassette (ABC) transporters. It was observed that when some ABC transporters have a high expression in leukemia cells, the prognosis of patients with AML is reserved as the response to treatment is inadequate. (de Jonge-Peeters et al., 2007)

The most studied transporter is the P-glycoprotein transporter (P-gp) - an ABC transporter responsible for unidirectional transmembrane translocation of the substrate (Gayet et al., 2005). P-gp is frequently involved in the emergence of multidrug resistance during chemotherapy (Shu & Liu, 2007). The multidrug resistance gene encodes this membrane transporter. Not only P-gp occurs in CH homeostasis at the cellular level, but also the synthesis of CH and CH-esters affects ATP-ase (Bucher et al., 2007) and the transmembrane transport by P-gp (Bucher et al., 2007; Shu & Liu, 2007). The lipid structure of the cell membranes also depends on the P-gp function (Dos Santos et al., 2007).

The ATP-ase activity of P-gp is controlled linearly by CH of the membrane structure. On the other hand, the decrease of membrane CH correlates with the non-linear decrease of the daunorubicin efflux induced by P-gp. An effective way to raise awareness of ALL CEM resistant to chemotherapy cells consists of partial depletion of the CH from cell membrane structure, that lowers the daunorubicin efflux by P-gp. (Gayet et al., 2005)

CH is able to increase basal activity of P-gp ATP-ase and increase P-gp sensitivity to progesterone and verapamil, modulators of this transporter. (Bucher et al., 2007) LDL-cholesterol can enlarge P-gp expression. In an experiment conducted in vitro, HMG-CoA reductase inhibitors were added to a primitive leukemia cells line (KG1a) and the observation was that lovastatin caused a decrease of 26% of P-gp expression, and pravastatin - a decrease of 16 %. (Connelly-Smith et al., 2007) But the CH derived from LDL was also able to restore sensitivity to chemotherapy of a human lymphoblastic leukemia cell line. It seems that the mechanism explaining this return is the restoration of the membrane CH and the reducing of the P-gp-associated ATPase to the same level. (Shu & Liu, 2007) The changes of the membrane CH quantity may be responsible for P-gp inhibition. It was observed that disassembly of lipid rafts can be produced both by the decrease of the CH content and by its increase. For a normal capacity of P-gp transport it is necessary to maintain accurate properties of membrane structures known as lipid raft. (Dos Santos et al., 2007)

In a clinical trial involving patients with CLL the P-gp expression of lymphocytes from peripheral blood was determined flowcytometrically. Those patients whose lymphocytes expressed P-gp were treated for 6 days with 80 mg lovastatin daily, then a new sample of peripheral blood was examined flowcytometrically. Lymphocytes of six of the 27 studied

patients expressed P-gp; about 20% of them were positive. Following the administration of lovastatin only 7.33% of them also expressed P-gp ($p = 0.016$). Compared to the proportion of positive lymphocytes at baseline, the decline was of 63.35%. During the study, CH decreased statistically significantly, with 20.43%. There was no observation of the appearance of possible drug adverse effects. In conclusion, the 6 days therapy with lovastatin was able to reduce significantly the CH and the number of lymphocytes in the membranes where P-gp is expressed, so that this statin could contribute through its pleiotropic effects to reduce multidrug resistance, especially when it is followed by chemotherapy. (Mihăilă et al., 2010)

This drug efflux pump can be inhibited by verapamil, too, the research made in vitro proved that it can reduce multidrug resistance. In such a study conducted in two patients with leukemic lymphoma resistant to treatment, verapamil was able to increase the intracellular amount of doxorubicin (Tidefelt et al., 1994).

It was found that verapamil was able to overcome the P-gp - mediated resistance to doxorubicin and vincristine in a canine cell line of B cell lymphoma (GL-1) (Uozurmi et al., 2005, as cited in Mihăilă et al., 2008). These experimental findings were not confirmed by parallel administration of chemosensitizer verapamil to chemotherapy (cyclophosphamide, doxorubicin, vincristine, and dexamethasone) in patients with medium and high level NHL found in advanced stages. This drug combination did not increase the therapeutic response and did not extend the survival in these patients as compared to those treated only with the mentioned chemotherapy (without verapamil) (Gaynor et al., 2001, as cited in Mihăilă et al., 2008), but it cannot be excluded that it could be effective in some patients who develop multidrug resistance. But, in metastatic breast carcinoma that has become resistant to anthracyclines verapamil has showed that it is able to increase the survival of patients (Belpomme et al., 2000, as cited in Mihăilă et al., 2008). In the case of the patient described above with hypertension and primary mammary NHL, the evolution has been favorable under the combination of verapamil to chemo- and radiotherapy, that has resulted in a event-free survival of 6 years (up to the present day) (Mihăilă et al., 2008).

In another study, 45 patients with proliferative haematological disorders were included in one of the following two groups: A - those who had hypertension and who received verapamil + chemotherapy, and B - those with normal blood pressure, who received only chemotherapy. Group A included 7 patients with chronic lymphoproliferations and 2 with chronic myeloproliferations; under treatment, both systolic and diastolic pressure decreased significantly in all patients in the group. Initially the serum CH level was higher than in the patients in group B ($p = 0.004$), while other biological tests did not vary significantly between group A and B. No adverse effects were observed during the study. The fact that the initial blood CH was higher in patients in group A suggests that malignant cells of patients in group B captured more blood CH that contributed to their proliferation. Although the average survival was not significantly different between group A and B, in group A there were more patients with stable disease (77.78% versus 44.44% - $p < 0.0001$) while in group B more patients had progressive disease (30.56 % versus 11.11% - $p < 0.0001$). The deaths due to progressive disease were significantly more numerous in group B. The authors consider that verapamil is useful not only because of its antihypertensive effect, but also due to its pleiotropic effects through which it could influence the evolution of neoplasia by inhibiting P-gp function and the efflux of drugs from lymphoma or leukemia cells. (Mihăilă et al., 2008)

10. Conclusions

Various epidemiological studies have found that between blood lipids and various neoplastic diseases there are some correlations.

Some authors found that in patients with newly diagnosed NHL the blood levels of CH, phospholipids and HDL-cholesterol had lower values than those of controls and the values of CH increased progressively after chemotherapy if the disease reached complete remission or was stationary, unlike those with disease progression, that their blood lipid levels were even lower.

Nearly all the children with ALL when diagnosed and during chemotherapy revealed a predictable model of serum dyslipidemia that consisted of very low levels of HDL-cholesterol, and elevated TG, and LDL-cholesterol, that regained normal values during the remission period.

In children with ALL, treated with asparaginase, hypertriglyceridemia was frequently observed and it can be cause of acute pancreatitis and thrombosis.

Imatinib mesylate, used for the treatment of patients with chronic myeloid leukemia, led to a diminishing of serum CH and TG values and CH depletion can inhibit cell proliferation.

The young survivors of ALL, disease which they had in their childhood, especially those who received cranial radiotherapy, are likely to develop hyperlipidemia, insulin resistance, obesity, arterial hypertension and even MS soon after the treatment.

Cranial irradiation favors more the appearance of MS by GH deficiency, lower level of insulin-like growth factor 1, fasting hyperinsulinemia, abdominal obesity and hyperlipidemia, especially in women.

It is believed that CH is important for cell proliferation, because low serum CH values may be the result of high cellular CH need of cancerous cells. Low serum CH values correlate with elevated levels of CH in lymphocytes. Malignant, proliferative cells have an intense metabolism of CH, while decreased intake of CH is responsible for decreasing cell proliferation.

An increase of lipoprotein lipase mRNA levels is present in CLL patients with shorter survival.

CD5 antigen is responsible for CH synthesis and even for adipogenesis. It is known that malignant cells from CLL are undergoing a process of continuous stimulation due to CD5 activation and cell survival.

The loss of CH is responsible for the decrease in the number of sites that can fix some monoclonal antibodies, including CD20. Statins interfere with the detection of CD20 antigen as well as the antilymphomatous function of the rituximab, but this effect was not showed in some clinical studies.

Statins reduce cellular proliferation and stimulate apoptosis of cancerous cells. By their pleiotropic effects, statins can be useful in the treatment of different diseases, like NHL, CLL, multiple myeloma and AML, as adjuvant therapy.

The association of simvastatin with fludarabine or cladribine synergistically induces DNA damages, and these lead to apoptosis.

Statins are active also in acute promyelocytic leukemia cells, where they augment the antileukemic response that depends on all-trans retinoic acid.

The ATP-ase activity of P-gp, frequently involved in the emergence of multidrug resistance during chemotherapy, is controlled linearly by CH of the membrane structure. The changes of the membrane CH quantity may be responsible for P-gp inhibition.

This drug efflux pump can be inhibited by statins and verapamil.

By their pleiotropic effects, statins are useful not only for dyslipidemia treatment, but also in antineoplastic therapy.

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12. References

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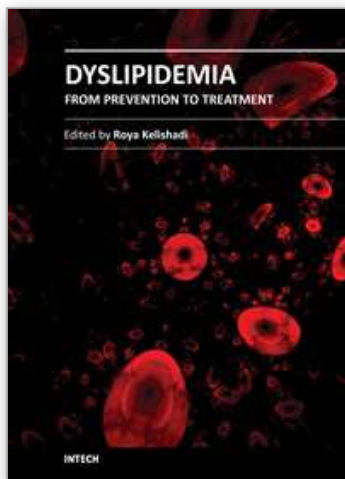
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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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