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Clinical aspects of prophylaxis and treatment of CNS disease in lymphoma patients

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ABSTRACT

Currently, infiltration of the central nervous system (CNS) in lymphoma patients is an unfavorable prognostic factor contributing to shorter survival. In these cases, immunophenotypisation has become important for evaluation of cerebrospinal fluid cells – especially in the so-called ''subclinical form of CNS involvement.'' Other methods used in these cases include diagnostic imaging and cytological examination. Therapy protocols, including the prophylactic intrathecal administration of drugs, are used for treatment of some lymphoma subtypes characterized by frequent CNS infiltrations, either at diagnosis or during relapse (lymphoblastic lymphoma/acute lymphoblastic leukemia, Burkitt's lymphoma, diffuse large B cell lymphoma, and lymphoma in HIV+ patients). In current clinical practice, prophylactic irradiation of the CNS is used less frequently. In addition to local treatment of the CNS, systemic therapy with high-dose methotrexate and cytosine arabinoside is recommended. The intrathecal treatment of choice is liposomal cytosine arabinoside or triple therapy: methotrexate, cytarabine, and dexamethasone. Because liposomal cytosine arabinoside has sustained activity in the CSF for 2 weeks, the number of intrathecal administrations necessary to eradicate CNS infiltrations may be reduced.

This paper summarizes our current findings and recommendations on the prevention and treatment of CNS involvement in lymphoma patients.

Central nervous system (CNS) involvement in lymphoproliferative tumors is considered a negative prognostic factor influencing shortened survival [1–3]. The pathophysiology of leukemic/lymphoma infiltrations in the CNS has not been sufficiently elucidated, despite progress in basic research. It is believed that leukemia cells can migrate from the skull bone marrow into the subarachnoid space through bridging veins and reach the cerebrospinal fluid through the choroid plexus, then penetrate into the brain tissue through the capillaries of the brain or infiltrate meninges through skull bone damage. Leukemia/lymphoma cells can also pass through nerve roots and occupy the subarachnoid space through nerve openings. Tumor masses can move into the epidural space through intervertebral spaces. Finally, the leukemic/lymphoma cells can infiltrate the CNS both through bleeding (if there are blasts in the blood) and in an

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iatrogenic way, during the traumatic diagnostic lumbar puncture. Symptomatology of changes is diverse, from the absence of clinical manifestations, when CNS involvement is detected incidentally during diagnostic puncture, to presentation of symptoms such as CNS bleeding, neurological deficits, or symptoms of spinal cord compression.

Diagnostic methods used in cases of suspicion of CNS infiltration

CNS involvement is most commonly diagnosed in the presence of clinical symptoms. These include headaches, behavioral disorders, cranial or peripheral nerve palsies, balance impairments, seizures, and coma. For diagnostic purposes, in addition to neurological examination, medical imaging is used, including: computed tomography, magnetic resonance, and more recently, positron emission tomography combined with computed tomography (FDG PET/CT). In each case of suspected CNS involvement, cerebrospinal fluid cytological assessment is recommended. Although this type of assessment is a highly specific method, it may give false-negative results in 20–60% of cases. Complementary methods to cytology include immunophenotyping and cytogenetic and molecular techniques [4–6]. Immunophenotyping of cerebrospinal fluid cells has its methodological limitations and requires proper technique of performance and analysis. The use of 11-parameter flow cytometry in a prospective evaluation of CNS involvement in patients with aggressive non-Hodgkin B-cell lymphoma led to a nearly fourfold increase in detection [7]. Detection in the CSF of more than 20% of the cells corresponding to the phenotype of B or T cell tumor cells is considered evidence of CNS infiltration [6].

Cerebrospinal fluid analysis with immunophenotypic characterization of cells is particularly useful in prevention of CNS infiltration in diffuse large B-cell lymphoma and other precursor B-cell lymphoid tumors with increased risk of CNS involvement [8]. Confirmation of the presence of tumor cells in the cerebrospinal fluid can also be obtained with the use of genetic analysis methods such as FISH. The presence of t(14;18), t(8;14), and DNA hyperdiploidy was found in cases of transformed follicular lymphoma and lymphoblastic lymphoma. In these cases, the coexistence of BCL6 and *c-MYC* rearrangement was found [6].

There have also been reports about the possibility of using biomolecular tests (such as PCR) in cerebrospinal fluid analysis. Identification of microRNA (MiR21, miR-19, and miR92a) by RT-PCR with 95.7% sensitivity and 96.7% specificity is considered as a new, noninvasive biomarker for diagnosis of primary central nervous system lymphoma (PCNSL) [9].

Progress in basic science, the implementation of new diagnostic methods to everyday clinical practice, and adjustment of therapy in the treatment of leukemia/lymphoma justify the need to analyze the methods of diagnosis and treatment for CNS involvement, as well as the previously used methods of prevention.

The incidence of CNS infiltration is different depending on the subtype of lymphoproliferative tumor. Such changes are most frequently observed in acute lymphoblastic leukemia and other aggressive lymphomas, and least frequently in indolent lymphomas and chronic lymphocytic leukemia (Table I).

Prevention and treatment of CNS infiltration in acute lymphoblastic leukemia in adults

Treatment of acute lymphoblastic leukemia (ALL) in adults can achieve complete remission (CR) in more than 74–92% of the patients with 5-year overall survival in approximately 37% [10–14]. In recent years, many research groups used ALL treatment protocols taking into account the so-called risk factors in patients. One of the factors with poor prognostic impact is CNS involvement both at diagnosis and during treatment [15]. CNS involvement at diagnosis is reported in

Table I – Incidence of infiltrates in the central nervous system in certain types of lymphoproliferative neoplasms (data from various publications, in the cited literature)

Diagnosis	The incidence at diagnosis	The incidence at relapse
Acute lymphoblastic leukemia	5%	Up to 50% in the absence of prevention Approximately 5–6%, despite prevention
Lymphoblastic lymphoma	2–7%	4.3% (with CHOP treatment and Mtx 12 mg IT prophylaxis)
Burkitt's lymphoma	App. 7%	24.4% (with: CHOP, Mtx 12 mg 6–8 applications IT, MTX 2.0 g/m^2 IV)
Diffuse large B-cell lymphoma	Often subclinical, the incidence difficult to determine	App. 5% (2.1–10.4%)
Aggressive lymphomas in HIV patients (DLBCL, Burkitt's, plasmoblastic, anaplastic)	3–15%	4–5% despite routine prophylaxis
Mantle cell lymphoma	0.9%	4.1% – in the course of the disease (no routine prophylaxis)
Chronic lymphocytic leukemia	Occasionally	Occasionally, usually at progression, Richter's transformation (low frequency)

approximately 3–7% of the patients. Risk factors for the occurrence of CNS leukemia are T-cell subtype, ''mature B cells'' phenotype, high leukocytosis in peripheral blood, mediastinal lesions, and elevated levels of serum LDH (1, www.nccn.org, NCCN Clinical Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia, Version I.2014, accessed on 25.11.2014). The published analysis of 380 ALL patients treated in prospective studies of the Polish Adult Leukemia Group (PALG) showed that primary CNS involvement was present in 5.3% of the patients [16]. In the absence of CNS-directed prophylaxis, CNS relapses may affect even 30–50% of patients and the five-year survival rate is less than 10% [17, 18]. For many years, an integral part of the programs of multidrug intensive ALL chemotherapy in adults has been CNS involvement prophylaxis. It is used regardless of ALL subtype, both in T and B cell tumors, in Philadelphia/BCR-ABL positive leukemia, and in Philadelphia/BCR-ABL negative leukemia, regardless of the age of the patient [19]. Prophylaxis involves administration of cytotoxic drugs directly into the cerebrospinal fluid, intravenous high doses of CNS-penetrating cytosine arabinoside and methotrexate, corticosteroids, and skull base irradiation. As a result, the CNS relapse rate in ALL is low and it is estimated at about 5–9% [16]. In everyday clinical practice, prevention of CNS infiltration in ALL has become a routine practice. Prophylaxis is applied in all stages of treatment, during the induction, consolidation, and during maintenance therapy. It is also recommended in patients after bone marrow transplantation, mainly after autologous hematopoietic cell transplantation (www.palg.pl, Grupy Robocze, ds leczenia ostrej białaczki limfoblastycznej, PALG ALL6 protokół, accessed on 25.11.2014). Published data from prospective studies typically concern triple therapy (with the use of 40–50 mg cytosine arabinoside, 15 mg methotrexate, 4 mg dexamethasone). The number of applications of intrathecal drugs into the cerebrospinal fluid during lumbar puncture is different in various research protocols and ranges from 7–8 (PALG protocols) to 12–14 (Northern-Italian Leukemia Group – NILG, German Multicenter Study Group for Adult ALL – GMALL). Currently, the use of liposomal cytosine arabinoside is preferred in clinical practice [20, 21], which allows a reduction in the number of punctures, thus increasing adherence to ALL treatment protocols. Reported toxicity when the DepoCyte was administered concomitantly with high-dose systemic chemotherapy advised the carefulness with this combined treatment. In the paper serious unexpected neurotoxicity during hyper-CVAD treatment was reported and liposomal cytarabine IT administration 16% of patients experienced serious neurotoxicity [22].

In the global NCCN guidelines, CNS prophylaxis is a mandatory element of intensive ALL therapy in children and adults (www.nccn.org NCCN Clinical Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia, Version I.2014, accessed on 25.11.2014). The risk of CNS recurrence can be evaluated based on the degree of blastosis increase in the cerebrospinal fluid (CNS1 – no blasts in the cerebrospinal fluid, CNS2 – <5 cells per μl, CNS3 – ≥ 5 cells per μl). In 2008, PALG published recommendations for CNS prophylaxis policy for ALL in adults [16]. The recommendations concerning drugs for CNS prophylaxis, based on some publicized clinical observations also including the authors experience, proposed the administration of liposomal cytosine arabinoside (DepoCyte) instead of triple therapy [20, 23]. Long-term (2 weeks) maintenance of the drug in the cerebrospinal fluid allowed for a reduction of the number of prophylactic punctures during intensive treatment. This makes it even more crucial that hemostasis is maintained when performing a lumbar puncture; platelet count should exceed 50 G/l and anticoagulants should not be used [21]. Current PALG recommendations (www.palg.pl, Grupy Robocze, ds leczenia ostrej białaczki limfoblastycznej, PALG ALL6 protokół, accessed on 25.11.2014; ALL-6 PALG protocol) recommend 5 intrathecal drug applications during induction and consolidation therapy and every 3 months during the first year of maintenance therapy. The use of DepoCyte in prevention reduces the risk of complications by reducing the number of lumbar punctures and contributes to the strict adherence to the therapy regimen. Although there are no published results of ongoing prospective controlled trials comparing the effectiveness of triple prophylaxis (12 doses of methotrexate, cytarabine, and prednisolone) with DepoCyte monotherapy (6 doses in B-cell subtype and 8 doses in T-cell subtype; research conducted by the European LeukemiaNet, ALL-NILG 10/07 protocol, www.leukemia-net.org/www.leukemia-registry.eu), with the newly developed recommendations, some research groups prefer the use of liposomal cytosine arabinoside. CNS prophylaxis therapy with liposomal cytarabine in elderly patients in a prospective GMALL study proved to be effective and well tolerated [24].

CNS irradiation is becoming less popular in CNS prophylaxis; although this procedure is still under discussion, the increasing proportion of patients for whom hematopoietic cell transplantation is planned and where the optimal conditioning treatment in ALL is total body irradiation (TBI), CNS prophylaxis should not include irradiation. Therefore, properly conducted CNS preventive cytostatic treatment is becoming more important [25].

CNS recurrence in ALL may be isolated or occur in parallel with the overall activity of leukemia. Isolated CNS recurrence of leukemia usually precedes systemic recurrence. Changes are located mostly within the meninges. However, infiltrates may occur in brain tissue, making the efficacy of intrathecally administered drugs lower due to suboptimal brain penetration. In these cases, the treatment of choice is high doses of intravenous methotrexate or cytosine arabinoside and liposomal cytosine arabinoside administered into the cerebrospinal fluid. DepoCyte has extended activity both in the entire space of the spinal cord and in brain fluid chambers (Table II).

In the treatment of CNS leukemia, most frequently manifested by meningeal involvement, the same drugs are used as in prophylaxis. Triple therapy (methotrexate, cytosine arabinoside, dexamethasone) is routinely administered into the cerebrospinal fluid at intervals of several days by lumbar puncture of the intervertebral space, in practice, at least 2–3 times a week. The currently accepted treatment, with high clinical efficacy, is liposomal cytarabine [18, 26, 27]. Because of its long-lasting presence in the cerebral spinal fluid (2 weeks), cytosine arabinoside may be administered every two

Table II – Drugs used in prophylaxis and treatment of CNS involvement in lymphoproliferative neoplasms

Drug	Prevention of CNS involvement	Treatment of CNS infiltrations
Intravenous cytosine arabinoside – doses >0.5–1.0 g/m^2	In monotherapy	Frequently in monotherapy
Methotrexate intravenously – doses >1.0 g/m^2	In monotherapy	Frequently in monotherapy
Intrathecal cytosine arabinoside, 40–50 mg dose	In monotherapy or in combination with prednisone 40 mg, dexamethasone 4 mg, and methotrexate 12–15 mg (triple regimen)	In monotherapy or in combination with prednisone/dexamethasone and methotrexate (triple regimen); 2–3 doses per week
Intrathecal methotrexate 12–15 mg dose	In combination with prednisone/ dexamethasone (dual regimen) or additionally with cytosine (triple regimen)	In combination with prednisone/ dexamethasone and cytosine arabinoside (triple regimen)
Cytosine arabinoside – liposomal (DepoCyte) 50 mg dose	In monotherapy or in combination with dexamethasone 4 mg used during a single IT puncture (note: the drugs in separate syringes)	In monotherapy or in combination with dexamethasone, every 2 weeks until eradication of pathological pleocytosis followed by 2 additional doses
Radiation therapy to skull base and medulla oblongata/CNS (in adults also used less frequently)	Procedure of choice, supplementing chemoprophylaxis in patients not eligible for bone marrow transplant with TBI preparation	Procedure of choice, usually in lack of effect of aforementioned chemotherapeutic treatment

weeks. This treatment is well tolerated and neurological complications are relatively rare, as also confirmed in Polish observations: in 56% of the treatments, there were no adverse clinical effects, while severe headaches and fever occurred in 7% of the cases [28, 29]. Observations from a European multicenter phase II trial (GMALL) have shown that the use of liposomal cytarabine with dexamethasone prophylaxis (administered intrathecally or as a systemic treatment for 2 weeks) resulted in total remission in the CSF in 86% of the patients with ALL and in 40% of the patients with Burkitt's lymphoma. Side effects were observed in 89% of the patients, mainly headaches: III–IV grade headaches occurred in 32% [26]. Intrathecal treatment can be completed if in two consecutive punctures the cerebrospinal fluid is negative for blasts. Continuation of maintenance treatment is then recommended with prolonged intervals between IT drug administrations; however, the duration of CNS maintenance therapy has not been determined. The use of radiotherapy for CNS treatment is recommended in cases with a lack of chemotherapy effect and as the treatment of choice when infiltrates are present in brain tissue.

Prevention and treatment of CNS infiltration in lymphoblastic lymphoma and Burkitt's lymphoma

In the treatment of highly aggressive lymphomas, intensive induction chemotherapy is used together with prevention of CNS involvement. Principles of treatment are similar to ALL. Prophylaxis of CNS infiltration involves administration of high doses of CNS penetrating cytostatics and administration of drugs into the cerebrospinal fluid (triple therapy of choice or liposomal cytosine arabinoside). CNS irradiation is not recommended. Treatment of CNS infiltration by lymphoma is carried out in the same way as in treatment of ALL. In cases of resistance to the chemotherapy of choice, CNS irradiation can also be used [29, 30].

Treatment of CNS infiltration in mature B-cell neoplasms

Both primary and secondary involvements by mature B-cell lymphomas occur sporadically. In recent years, the need for a detailed assessment of the increased risk of CNS infiltration by large B-cell lymphoma (DLBCL) is emphasized.

In 2010, the Polish Lymphoma Research Group and the PALG published recommendations presenting an algorithm for diagnosis and therapy of patients with DLBCL [8]. Primary CNS involvement in DLBCL is rare; the estimated incidence of recurrence in this location is about 5%. Increased risk factors for CNS involvement are: raised LDH level, involvement of at least 2 extranodal sites, and involvement of so-called specific sites (testis, mammary glands, orbit, paranasal sinuses, and the spine). The risk of CNS involvement is enhanced in the primary mediastinal large B-cell lymphoma (PMLBCL) and intravascular large B-cell lymphoma [17]. The published Polish guidelines focus on the use of flow cytometry in cerebrospinal fluid evaluation for detailed diagnosis in patients with no neurological signs and the presence of at least one of the risk factors. In the case of PMLBCL and intravascular large B-cell lymphoma, as well as in DLBCL with at least two risk factors, intrathecal administration of drugs is recommended prophylactically during the first lumbar puncture. In CNS involvement, prophylaxis liposomal cytosine arabinoside or 15 mg methotrexate is recommended. Good efficacy and low toxicity of DepoCyte in prevention, assessed in the observation of 79 patients treated in two Polish centers [31], encourage the use of this drug in everyday clinical practice. However, in some publications neurotoxicity was reported: four of the fourteen patients (25%) developed grades 2 and 3 neurotoxicity manifested as conus nedullaris/cauda equine syndrome [32]. In cases where lymphoma cells are detected in the cerebrospinal fluid by flow cytometry, continuation of intrathecal treatment is recommended in

parallel with systemic therapy, and use of liposomal Ara-C is preferred due to favorable published clinical observations and the smaller number of lumbar punctures required for effective treatment [8].

In lymphocytic lymphoma/chronic lymphocytic leukemia (CLL/SLL) with CNS involvement in the form of meningeal infiltration, symptoms of systemic progression and Richter's transformation are often present. The analysis of 2514 Norwegian patients with various lymphoma subtypes showed that the frequency of CNS low-grade recurrence in NHL according to the Kiel classification (time period of analysis: 1980–1996) was 2.8% within five years, compared to 4.3% in the high-grade lymphomas and 24.4% in Burkitt's lymphoma or lymphoblastic lymphoma [33]. In multivariate analysis, independent risk factors for CNS involvement were B symptoms, bone marrow involvement, and skin involvement. The coexistence of two/three of these factors in low-grade lymphoma increased the risk of CNS involvement to about 7% in the 5-year follow-up. This is one of the limited data showing the incidence of CNS involvement in CLL. Due to the low incidence of CNS involvement in the course of CLL/SLL, prophylactic administration of intrathecal drugs is not recommended. However, treatment of CNS involvement is based on the general rules applicable to other subtypes of lymphoma, but reports of efficacy are case reports [34].

Observations of the Spanish group published in the British Journal of Hematology in 2010 concerning effective treatment of intrathecal liposomal cytarabine, the possibility of using a modern, effective therapy was indicated in 7 cases of meningeal involvement in Richter's syndrome. On average, 5 doses of intrathecal liposomal cytarabine (range 2–9) were used to obtain blast cell clearance in the cerebrospinal fluid. Only 3/7 of them had previous triple intrathecal therapy or CNS irradiation [33]. In another published case on the effective use of liposomal cytarabine in the treatment of CNS, recurrence preceding systemic recurrence in CLL lasting over 10 years, the use of liposomal cytarabine as consolidation and maintenance treatment allowed long-term maintenance and complete remission within the CNS [35].

Mantle cell lymphoma – localization of changes in the CNS

Interesting observations concerning CNS involvement in mantle cell lymphoma (MCL) were presented in the analysis of the European Mantle Cell Lymphoma Network (EMCLN) involving 1396 patients with MCL [36]. The incidence of CNS involvement at diagnosis was 0.9% (0.5–1.6%, $n = 13$) and 4.1% over the course of the disease (3.2–5.2%, $n = 44$). Only 15 cases had isolated CNS involvement. The median follow-up of patients with CNS involvement was 17 months (0.2–170). The major high-risk factors were blastoid subtype (28% of patients with CNS involvement), the presence of general B symptoms (53%), clinical stage IV (91%), high MIPI (61%), and elevated LDH activity (75%). In 37%, CNS recurrence was isolated and in 63%, coexisted with systemic recurrence. In most cases of treatment of CNS involvement, systemic chemotherapy was used (72%). In 13%, combination with radiation was used, in 4%, only radiation was used, and in 10%, palliative treatment was used. The most commonly used drugs were: high-dose methotrexate, cytosine arabinoside (either alone or in multidrug regimens), a combination of rituximab with chemotherapy, and in 79%, the use of intrathecal therapy (triple, dual or single agent: methotrexate or liposomal cytarabine). The median overall survival from diagnosis of CNS involvement was 3.7 months (0.2–69.3). Some patients achieved complete remission within the CNS. The overall survival was 3.9 months, but some patients lived over 2 years [36].

CNS involvement in MCL is rare, but its occurrence is associated with poor prognosis. Until results of the prospective study are obtained, there are no clear rules concerning the prevention of CNS involvement in this disease.

Autotransplantation of hematopoietic cells in lymphomas with CNS involvement

Secondary CNS involvement in the course of lymphoma is, in most cases, associated with poor prognosis and reduced survival. The use of intensive induction chemotherapy based on high doses of methotrexate and cyclophosphamide with dexamethasone in combination with intrathecal administration of liposomal cytarabine prior to autologous hematopoietic cell transplantation (phase II prospective study, for conditioning treatment thiotepa and BCNU were used) resulted in CR in 63% of the patients with a 2-year Time to Treatment Failure (TTF) rate of $58 \pm 22\%$ [37]. This procedure may be used in everyday clinical practice as a treatment of choice.

Non-Hodgkin lymphoma in patients with HIV infection and CNS involvement

Patients with HIV infection have an increased incidence of lymphoma and a high grade of disease is indicated in these patients when initial clinical symptoms present. At diagnosis, most patients are in CS III/IV and in >70–98%, there is involvement at extranodal sites, mainly in the gastrointestinal tract, bone marrow, and CNS [38]. CNS involvement at diagnosis ranges from 3 to 15% and is most common in Burkitt's histological subtype in cases of extranodal site involvement and during the use of antiretroviral drugs. CNS involvement is often asymptomatic. Taking into account the high risk of progression in the CNS during treatment or recurrence in this location during NHL remission, a mandatory part of lymphoma treatment protocols in HIV patients includes use of intrathecal CNS prophylaxis. Based on the literature data on the low toxicity and good efficacy of intrathecal DepoCyte, a prospective analysis was performed in 30 patients with NHL treated with HAART. The number of intrathecal applications of liposomal cytarabine varied depending on the type of systemic chemotherapy used. With polychemotherapy regimens: Rituximab + Cyclophosphamide + Adriblastin + Oncovin + Prednison (R-CHOP), CHOP, and Rituximab + Cyclophosphamide + Doxorubicin + Etoposide (R-CDE) and the ''Stanford chemotherapy'' regimen the drug was

administered intrathecally every 3 weeks up to 6 applications IT, but of each R-CODOX-M systemic polychemotherapy cycle, up to 3 applications. Due to accumulation of toxicity during concomitant systemic use of high doses of Ara-C in the course of the "R-IVAC" cycles, DepoCyte was not administered intrathecally. Such a procedure was considered effective prophylaxis, despite the reduction in the number of intrathecal applications of drugs compared to triple prophylaxis regimen. CNS relapses occurred in 3% of the patients and the incidence did not differ from the general population of patients with lymphoma. In cases of lymphoma in HIV patients, the use of liposomal cytarabine as the agent of choice both in prophylaxis and treatment of CNS involvement is preferred [38].

In recent years, there have been numerous publications on the diagnosis and treatment of primary lymphoma of the brain. The standard first line therapy is the use of systemic high-dose methotrexate and cytarabine [39–41]. According to published observations of Sierra Del Rio, the prophylactic use of intrathecal drugs had no effect on improvement of therapy effectiveness [42]. Therefore, in everyday clinical practice, neither the prophylactic administration of cytostatics into cerebrospinal fluid nor prophylactic radiotherapy is used. Clinical observation reported 24% occurrence of the serious neurotixic side effect during the treatment with high-dose systemic methotrexate and Ara-C based polychemotherapy combined with liposomal Ara-C [43]. Conclusions based on small number of patients and should be confirmed on the larger group of the patients. In resistance and relapses, DHAP and ESHAP ± rituximab are recommended as salvage therapies, which resulted in response in about 27% of the patients. CNS irradiation was used to treat chemotherapy-resistant cases [44]. Another proposed approach is the use of consolidation treatment with high-dose chemotherapy (the use of BCNU and thiotepa is recommended in conditioning) with autologous hematopoietic cell transplantation. This treatment led to 5-year survival in more than 80% of the patients [45].

Despite the higher costs of liposomal cytarabine, the treatment is comparable in efficacy and according to the clinical experience of the authors and can be considered as treatment of choice because lower number of intrathecal doses give the same results which can improve the quality of life of oncologic patients. The total costs of intrathecal therapy using liposomal Ara-C can be even lower due to reduced cost of hospitalization and concomitant therapy during the treatment. Up to now pharmacoeconomic analyses of the problem are not available.

Summary

1. Prevention of CNS involvement is a fundamental element of intensive treatment of neoplasms originating from precursor B and T-cells (acute lymphoblastic leukemia/lymphoblastic lymphoma) and Burkitt's lymphoma.
2. In cases of large B cell lymphoma (DLBCL), the risk of CNS involvement should be assessed. When increased risk factors occur, it is advisable to prevent CNS infiltration with intrathecal administration of drugs.
3. Prevention of CNS involvement is recommended in all cases of lymphoma in HIV-positive patients, wherein the use of liposomal cytosine arabinoside is preferred.
4. In the treatment of CNS involvement in tumors of the lymphatic system, the administration of liposomal cytosine arabinoside shows the same efficacy as intrathecal triple therapy with fewer intrathecal punctures and comparable or lower toxicity but the neurologic complications after the treatment must be considered as well, especially during the concomitant systemic therapy.
5. Based on the published results of the clinical experience and retrospective analysis, the use of liposomal cytosine arabinoside is recommended in the prevention of CNS involvement.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

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Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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