ORIGINAL ARTICLE

Central nervous system prophylaxis with intrathecal liposomal cytarabine in diffuse large B-cell lymphomas

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KEY WORDS

central nervous system prophylaxis, liposomal cytarabine, non-Hodgkin lymphoma

ABSTRACT

INTRODUCTION Central nervous system (CNS) involvement is a serious and potentially fatal complication in patients with lymphoma because it is associated with a particularly poor prognosis (median progression-free survival [PFS] of 4–6 months). Although CNS prophylaxis is considered necessary, there are no clear guidelines on identifying high-risk patients or selecting treatment regimen.

OBJECTIVES The aim of the study was to assess the safety and efficacy of CNS prophylaxis with intrathecal liposomal cytarabine.

PATIENTS AND METHODS We analyzed the data of 79 patients (46 men and 33 women; median age, 48.5 years [20–79]) with diffuse large B-cell lymphoma (83.5% of the patients) and primary mediastinal large B-cell lymphoma (16.5%). Patients were treated in the departments of hematology in Kraków and Wrocław, Poland, between the years 2009–2012. They were considered to be at a high risk of developing CNS involvement associated with a lymphoma.

RESULTS Adverse reactions after intrathecal liposomal cytarabine were reported in 59 patients (74.7%); in 7 cases, the reactions were severe. The most common side effect was headache (67.1%). During antilymphoma therapy and prophylaxis, the functional status assessed by the Karnofsky score improved in 56 patients (70.9%) and remained unchanged in the remaining cases. A median follow-up time did not exceed 28 months (range, 1.4–52.1); during follow-up, neither median overall survival (OS) nor PFS were reached (projected OS and PFS at 48 months are 86.1% and 90.1%, respectively).

CONCLUSIONS Our results encourage the use of intrathecal liposomal cytarabine in CNS prophylaxis in patients with lymphoma.

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INTRODUCTION Central nervous system (CNS) involvement is a serious and potentially fatal complication in patients with lymphoma. In rare, highly aggressive B-cell malignancies, including Burkitt's lymphoma and lymphoblastic lymphoma, CNS prophylaxis is a widely accepted standard of care. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of the lymphoma (about 31% of all non-Hodgkin lymphomas in Western countries),[1] with a 2% to 15% risk of CNS involvement.[2] DLBCL comprises a quite complex group of lymphoid malignancies, which in the 2008 World Health Organization (WHO) Classification[1] was further subdivided into specific disease entities, well-characterized by their morphological, immunophenotypic, and molecular properties. Primary mediastinal large B-cell lymphoma (PMBCL) has been classified as a separate and well-defined clinico-pathological entity among DLBCLs (constituting about 2% of non-Hodgkin lymphomas), with unique clinical and biological characteristics,[3] including even more frequent CNS dissemination.[4] The median age of DLBCL at diagnosis falls between the sixth and seventh decade, while PMBCL manifests at a lower median age – between the second and third decades.[2]

TABLE Characteristics of the study groups

Variable		All patients (n = 79)	Patients with PMBCL (n = 13)	Patients with DLBCL (n = 66)
age, y		48.5 (20–79)	40.5 (28–57)	50.1 (20–79)
men, n		46 (58%)	7 (53%)	39 (59%)
men, age, y		48.5 (21–79)	41.7 (28–57)	49.7 (21–79)
women		33	6	27
women, age, y		48.5 (20–76)	39.2 (30–57)	50.6 (20–76)
systemic therapy	R-CHOP	77 (97.5)	13/100	64 (96.9)
	R-CVP	2 (2.5)	0	2 (3.0)
	ASCT	9 (11.4)	4 (30.7)	5 (7.6)
systemic progression		5 (6.3)	1 (7.7)	4 (6.1)
cardiac comorbidities		2 (2.5)	0	2 (3.0)
deaths		5 (6.3)	1 (7.7)	4 (6.1)
CSF cells, n of cells/μl		3.7 (0–15)	3.46 (1–7)	3.74 (0–15)
DepoCyte injections		3.4 (1–7)	3.6 (1–7)	3.3 (1–7)
risk factors	LDH, U/l	735.3 (168–7401)	812.7 (284–4200)	720.0 (168–7401)
	elevated LDH	51 (64.6)	5/46.1	45 (68.2)
	IPI (3–5)	49 (62.0)	4/30.8	45 (68.2)
	≥ extranodal sites	33 (41.7)	3/23.1	30 (45.5)
	infiltration of specific sites[a]	36 (45.6)	10/76.9	26 (39.4)

All continuous variables were presented as means (ranges) and dichotomous variables as number (%).

a patients with involvement at specific sites, including infiltration of the vertebral column, orbits, sinuses, or testes

Abbreviations: ASCT – autologous stem cell transplantation, CNS – central nervous system, CSF – cerebrospinal fluid, DLBCL – diffuse large B-cell lymphoma, IPI – international prognostic index, LDH – lactate dehydrogenase, PMBCL – primary mediastinal large B-cell lymphoma

Immunochemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), recycled every 14 to 21 days, is regarded as a gold standard in both DLBCL and PMBCL.[5,6] In the rituximab era, treatment outcomes have improved. Progression-free survivals (PFS) have been obtained in 80% to 85% of the patients with low-risk disease, and over 60% of those in an advanced stage.[2] However, none of the drugs included in the R-CHOP protocol penetrates the brain–blood barrier; therefore, the issue of CNS prophylaxis must be addressed separately.

CNS dissemination in DLBCL and PMBCL is associated with a particularly poor prognosis (median PFS of 4–6 months).[7] Furthermore, there are no clear guidelines either for selection of patients who should receive prophylaxis or for the choice of the recommended regimen. As effective CNS prophylaxis also induces adverse reactions, it should be offered only to selected patients. High risk according to the international prognostic index (IPI) correlates with the risk of CNS involvement: in one of the larger analyses, the risk of CNS involvement, which is low in cases with an age-adjusted IPI of 0 to 1 (0%–0.5%), increases in patients with an age-adjusted IPI of 2 to 3 (4.5%–9.7%).[8] Increased serum levels of lactate dehydrogenase (LDH) and the involvement of more than 1 extranodal site are regarded as independent risk factors, together with infiltration of "specific sites" (testicles, orbits, paranasal sinuses, paravertebral areas),[2] involvement of the bone marrow, systemic relapse,[9,10] poor performance status, and failure to attain remission.[11,12]

In this paper, we report the experience of 2 centers in CNS prophylaxis with liposomal cytarabine in patients with DLBCL and PMBCL treated with R-CHOP. Liposomal cytarabine (Depocyte®, Mundipharma International Limited) is a sustained-release formulation of cytarabine developed for intrathecal administration, ensuring prolonged cytotoxic drug concentrations of cytarabine in the cerebrospinal fluid (CSF). It has been approved for treatment of leptomenigeal dissemination in patients with leukemia and lymphoma. Its efficacy has been confirmed in acute lymphoblastic leukemia, Burkitt's lymphoma, and unclassifiable highly aggressive B-cell lymphomas.[13,14] Compared with intrathecal cytarabine, intrathecal liposomal cytarabine showed a significantly higher response rate, a greater improvement in the quality of life,[13] and in the quality of life-adjusted survival.[15] A significant risk of CNS dissemination in selected DLBCL cases and severity of this complication justify the use of this treatment strategy as prophylaxis. This idea is reflected by an increasing use of liposomal cytarabine for prophylaxis in numerous studies.[16-18]

The Polish Lymphoma Research Group and Polish Adult Leukemia Group recommend intrathecal liposomal cytarabine in prophylaxis of high-risk patients with DLBCL.[19] However, data on its safety and efficacy in prophylactic therapy in DLBCL and PMBCL are still insufficient.[17] The present study reports data on one

of the largest groups of patients after prophylactic treatment with liposomal cytarabine. We believe that our findings will provide the groundwork for future third-phase trials.

PATIENTS AND METHODS The study group consisted of 79 consecutive patients with DLBCL (83.5%; n = 66) and PMBCL (16.5%; n = 13) diagnosed and treated in the Department of Hematology in Kraków (n = 74) and Wrocław (n = 5) between 2009–2012, and considered to be at a high risk of developing CNS involvement. All patients received systemic chemotherapy according to the R-CHOP protocol as well as intrathecal liposomal cytarabine as CNS prophylaxis (TABLE).

In all cases, the diagnosis of a lymphoma was based on histopathological samples according to the WHO classification, including necessary immunohistochemical stains,[1] in specialized hematopathology laboratories.

Patients were considered as having a high risk of CNS involvement based on the identification of 1 of 2 main factors. The first one was a specific site of the lymphoma (testicles, sinuses, orbits, or paravertebral infiltration), diagnosed by computer tomography (CT), magnetic resonance imaging, or positron emission tomography CT (PET-CT). The second one was the presence of 2 widely accepted risk factors: increased LDH, IPI of 3 to 5, and/or 2 or more extranodal sites. Normal LDH levels vary between laboratories and changes over time, in our study, the borderline level was established at 480 U/l. At the beginning of the study, we regarded the diagnosis of PMBCL as necessitating CNS prophylaxis; however, a retrospective analysis demonstrated that all of the patients with PMBCL had to be regarded as high-risk for other reasons. Patients with any neurological signs and symptoms at diagnosis, abnormalities in CNS imaging studies suggesting lymphoma infiltrations, or increased pleocytosis (>15 cells/μl) in a cytological analysis of CSF were excluded.

The R-CHOP regimen (rituximab [MabThera®, Roche, Switzerland], 375 mg/m^2; cyclophosphamide [Endoxan®, Baxter, Switzerland], 750 mg/m^2; doxorubicin [ADM-Doxorubicin®, Medac, Germany], 50 mg/m^2; vincristine [Vincristine®, Gedeon Richter, Hungary], 2 mg IV at day 1; prednisone [Encorton®, Polfa Pabianice S.A., Poland], 100 mg/d orally at days 1–5) was administered every 21 days (DLBCL) or 14 days (PMBCL). In cases with cardiac comorbidities, a doxorubicin dose was reduced and, in some patients, omitted. Consolidation radiotherapy was regarded mandatory for all PMBCL patients, those with refractory or relapsed disease were considered for autologous stem cell transplantation.

CNS prophylaxis (intrathecal liposomal cytarabine) was combined with systemic chemotherapy, which was administered every 2 to 3 weeks. The lumbar puncture was performed after infusion of systemic immunochemotherapy, usually in the afternoon hours. We observed frequent failures in receiving CSF in the morning hours (adequate hydration is necessary to complete the procedure). All patients received oral prednisone (as an element of the R-CHOP regimen) on administration of intrathecal liposomal cytarabine and remained in a horizontal position for 6 h after the procedure to minimize the possibility of side effects.

At each chemotherapy cycle, medical history, physical and neurological examination, biochemistry, full blood count, and CSF cytological examination were performed. Adverse reactions were recorded (according to version 4.0 of the Common Terminology Criteria for Adverse Events of the National Cancer Institute, NCI-CTCAE v 4.0). At baseline and at the end of treatment, we also evaluated patients' performance status according to the Karnofsky score. Staging and effectiveness of systemic therapy was assessed by CT or PET-CT imaging at diagnosis, after the third or fourth chemotherapy cycle, and at the end of the therapy. All patients were followed up for PFS, overall survival (OS), and CNS relapse at least every 6 months.

A statistical analysis was performed with the use of the Statistica 10.0 software (StatSoft, Germany). Continuous variables were expressed as means (with range values), while dichotomous variables were expressed as number or percentage. A survival analysis was performed with the Kaplan–Meier estimation. Correlation calculations on ordinal variables were done with the Spearman's rank correlation coefficient (Spearman's rho).

RESULTS The study population consisted of 79 patients (46 men and 33 women) with a medium age of 48.5 years (20–79) lowered substantially in the subgroup with PMBCL (13 cases with a median age below 40.5 years). The average cell count in CSF at diagnosis was 3.67/μl (range, 0–15). The characteristics of the study population are presented in TABLE.

Patients in the study population were classified as high-risk according to the following criteria (TABLE): specific site (n = 36, 45.6%) including testicles (n = 5), paravertebral areas (n = 12), bone marrow (n = 7), sinuses (n = 6), and orbits (n = 6); presence of 2 or more risk factors (n = 52, 65.8%) including elevated LDH levels (n = 51), IPI of 3 to 5 (n = 49), and 2 or more extranodal sites (n = 33). All 3 risk factors were observed in 16 cases; 11.4% of the patients (n = 9) fulfilled both criteria (specific site infiltration and 2 or more risk factors). Patients with PMBCL (n = 13) had either infiltrations of the paravertebral areas (n = 6), other specific site (n = 4), or had 2 or more risk factors (n = 4).

CNS prophylaxis was part of the first-line therapy: in 58 patients (73.4%), it was started with the first R-CHOP cycle and in 10 patients (12.6%) as the third or fourth chemotherapy cycle. In 11 cases, it was given after the end of the first-line therapy, also at 2- to 3-week intervals. In 73.4% of the study population, treatment was started

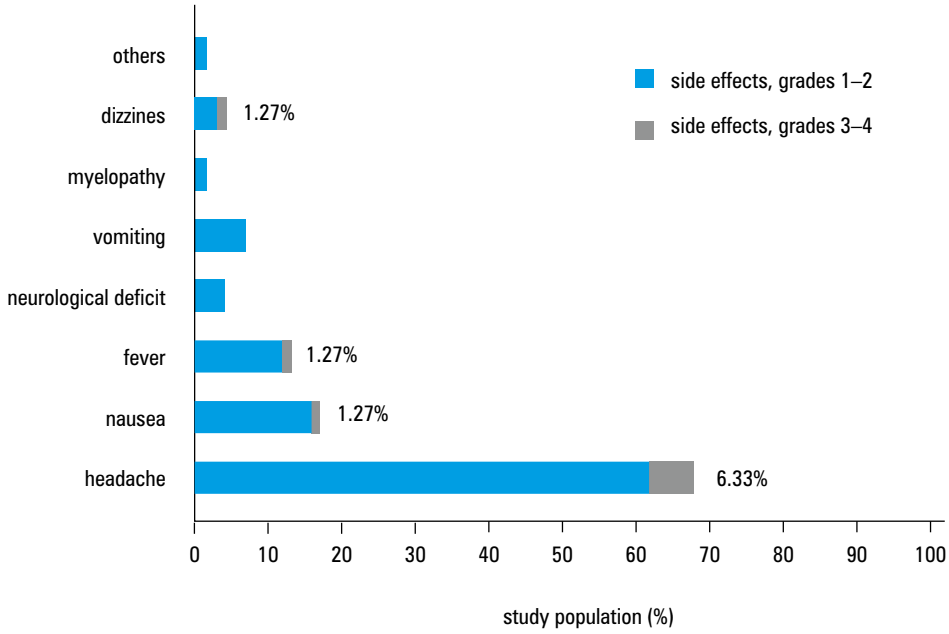

FIGURE 1 Frequency of adverse reactions after liposomal cytarabine administration in the whole study population graded according to CTACAE v. 4.0

within the first 50 days after diagnosis, in 86% within the first 100 days (range, 0–365 days; average, 50 days).

In our protocol, we aimed at administering 4 doses of liposomal cytarabine in each patient. In case of long-lasting or severe adverse reactions, a subsequent intrathecal injection was postponed until symptoms disappeared. The average number of DepoCyte injections was 3.38 (range, 0–7). Although it was our aim to give 4 injections of liposomal cytarabine, in 2 cases, 6 and 7 doses were administered owing to large tumor burden and physician judgment.

Adverse reactions after intrathecal administration of liposomal cytarabine were reported in 59 patients (74.7% of the study population), but in most cases they were mild (CTCAE grade, 1–2). Only in 7 cases, the reactions were severe (CTCAE grade, 3–4) (FIGURE 1). The most frequent side effect was headache; 53 patients (67.1%) suffered from at least 1 episode, regarded as severe (CTCAE, grade 3–4) in 5 cases. Other adverse reactions included nausea (16.5%), fever (12.7%), vomiting (6.3%), neurological deficits (3.8%), dizziness (3.8%), and myelopathy (1.3%). We did not identify any risk factors for those side effects; there were no statistically significant correlations between the presence or severity of side effects and any of the above high-risk factors, age, sex, or number of DepoCyte injections (Spearman's rho).

In 56 patients (70.9%), the functional status assessed by the Karnofsky score improved. In the remaining cases, it did not change during treatment.

At a median follow-up time of 28 months (range, 1.4–52.1), median OS and PFS were not reached. Projected PFS and OS at 48 months are 90.1% and 86.1%, respectively (FIGURE 2). All deaths (n = 5) were due to disease progression (n = 4) or cardiac complications (n = 1). None of the patients developed CNS involvement. Neurological episodes or abnormal cytological results of the CSF were not reported in any of the patients during therapy or follow-up.

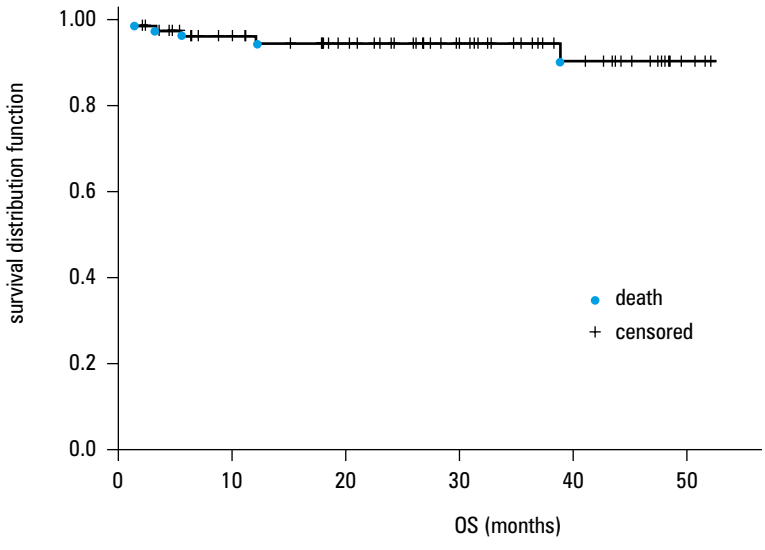

FIGURE 2 Overall survival (OS) in the study population; OS function was prepared with the Statistica 10.0 software, Kaplan–Meier estimation: cumulative percentage with event

DISCUSSION Lymphoma involvement of the leptomeninges (the pia mater and arachnoid membranes) and infiltrations of the brain itself are serious complications of DLBCL and PMBCL. The prognosis is particularly poor with a median survival from 4 to 6 weeks in untreated cases,[20] to 4 to 6 months in patients treated according to the current standards of care (radiotherapy and/or intrathecal or systemic chemotherapy).[7]

In the rituximab era, cure rates in DLBCLs have greatly improved. What is more, a few retrospective studies have reported that rituximab seems to prevent CNS relapse,[12] and its use may make CNS prophylaxis unnecessary.[11,21] Although rituximab with its poor penetration through the brain–blood barrier has little if any impact on lymphoma cells already present in CNS, it may decrease relapse rate in central nervous system by reducing the recurrence at all site.[9,10] CNS involvement determines the length of life in patients with

DLBCLs; that is why, prophylaxis in selected cases seems to be the treatment of choice.

Therefore, CNS prophylaxis of high-risk cases is required during first-line therapy of aggressive lymphoma subtypes. Historically, the first prophylaxis that was investigated was intrathecal methotrexate with or without cytarabine and hydrocortisone.[22] The main disadvantage of those short-acting drugs was the necessity to administer them frequently, 2 to 3 times a week. This regimen induced puncture stress, injection difficulties, and headache. The efficacy of this approach could have been further compromised by insufficient penetration to the brain tissue, owing to differences in drug concentrations, diminishing with the distance to the drug injection site. Prophylactic whole-brain radiotherapy, which is sometimes applied in lymphoblastic and Burkitt's lymphoma, has never been widely used in patients with DLBCL and PMBCL. Systemic chemotherapy with cytostatic doses penetrating the brain–blood barrier, that is, administered as an early consolidation, is rarely necessary. It is feasible only in younger patients, while the average age at DLBCL diagnosis is over 60 years. Of note, however, excellent results of a French randomized trial, with doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone chemotherapy regimen, in which CNS dissemination/relapse was below 2.7% compared with 8.3% for the CHOP protocol ($P = 0.002$).[23]

Randomized clinical trials demonstrated that intrathecal liposomal cytarabine, a formulation with prolonged half-life, is at least as effective as intrathecal methotrexate or cytarabine in patients with leptomeningeal metastases.[13,24] Moreover, formulation of liposomal cytarabine, which increases CNS bioavailability, extends half-life and decreases the number of the required lumbar punctures.[25] This treatment can improve not only the cure rate but also the quality of life (the drug is administered with concomitant chemotherapy, without the necessity of additional hospitalizations).

Liposomal cytarabine can result in significant neurotoxicity in some patients (2%–4% of the cases may demonstrate transitional or irreversible cauda equine syndrome).[26] In our study, adverse reactions were mild but relatively common, present in nearly 75% of the cases. We observed only 6 episodes of severe postdural puncture headache in 267 depocyte administrations (2.2%), presenting as severe headache, neck stiffness, nausea, and vomiting, which prolonged hospitalization. None of our patients developed irreversible neurological toxicity. It is probable that proper hydration, prolonged bed rest (6–12 h) in a horizontal position after the procedure, and concomitant oral steroids (as part of the R-CHOP protocol) decreased both the incidence and severity of adverse reactions. Similar results were reported by Garcia-Marco et al.[17] They used liposomal cytarabine to treat CNS involvement and observed side effects in 75.9% of the cases. Headache was the most frequent adverse reaction reported in 17 of 54 patients. Other symptoms included nausea (n = 7), fever (n = 7), vomiting (n = 6), neurological deficits (n = 2), dizziness (n = 1), and chemical arachnoiditis (n = 1).

The possibility of severe and potentially irreversible adverse reactions, unacceptable in the prophylaxis setting of low-risk cases, raises the issue of patient selection for liposomal cytarabine prophylaxis. In our group, it was based on the well-established risk factors; without CNS prophylaxis, CNS estimated dissemination/relapse rate would be as high as 8% to 15%. In retrospective analyses, CNS involvement was reported in 5.9% of 3258 lymphoma patients,[27] 10% of 403 high-risk cases,[10] and 6.5% in eldery patients.[28] None of our patients experienced CNS relapse within the median follow-up time of 28 months, which clearly demonstrates the efficacy of liposomal cytarabine in this setting. With acceptable rates of adverse reactions, it could become a new standard of care in high-risk cases.

The dose and frequency of liposomal cytarabine remains an open issue. Considering pharmacokinetic data, it is tempting to speculate that dose reduction to 25 mg would be equally effective (maximum concentration for a dose of 25 mg is 77 ±17 μg/ml and, for a dose of 50 mg, it is 73 ±11 μg/ml; there are also no significant differences in bio-distribution).[29] However, the drug is currently produced only in 50-mg vials. Moreover, the required number of liposomal cytarabine doses has not been established yet. At a recent advisory board discussion in Frankfurt, Germany, it has been postulated that 25 mg administered 3 times at 2- to 3-week intervals could reduce the adverse event rate without affecting efficacy (personal communication).

Our study has several limitations. It was a noncomparative, retrospective evaluation of unselected, consecutive patients treated with liposomal cytarabine in 2 hospitals in Poland. The retrospective method of data collection is subject to information gaps because not all data had been reported at the time of a clinic visit. Moreover, an institutional standard of care is not a substitute for a study protocol; therefore, patients were treated less consistently. Finally, there was no comparator arm and the results may only be discussed in relation to other patient series. We decided not to compare them with historical data from our institutions because patients had not received rituximab previously, which resulted in a worse systemic outcome. Our patients have an excellent outcome: the projected PFS and OS at 48 months of 90.1% and 86.1% of the cases, respectively, is higher than expected, which raises the question of patient selection bias. All the above arguments do not undermine the excellent efficacy and relative safety of prophylactic liposomal cytarabine regimen.

In conclusion, our study demonstrated the effectiveness of intrathecal prophylaxis with

liposomal cytarabine. No patients experienced a CNS event and we did not observe any symptoms of neurological involvement during a median follow-up time of 27 months. Finally, treatment was well-tolerated; if treatment-related toxicity was reported, it was generally of minor severity and could be reversed.

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ARTYKUŁ ORYGINALNY

Profilaktyka zajęcia ośrodkowego układu nerwowego przy użyciu liposomalnej cytarabiny w chłoniakach rozlanych z dużych komórek B

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chłoniak nieziarniczy, liposomalna cytarabina, profilaktyka centralnego systemu nerwowego

STRESZCZENIE

WPROWADZENIE Zajęcie ośrodkowego układu nerwowego (OUN) w przebiegu chłoniaków jest poważnym i potencjalnie śmiertelnym powikłaniem, gdyż charakteryzuje się szczególnie złym rokowaniem (mediana czasu wolnego od progresji [*progression-free survival* – PFS] to 4–6 miesięcy). Leczenie profilaktyczne zajęcia OUN wydaje się konieczne, jednak brakuje jasnych wytycznych co do identyfikacji pacjentów z grupy ryzyka oraz sposobu postępowania.

CELE Ocena bezpieczeństwa oraz skuteczności prowadzenia profilaktyki zajęcia OUN przy pomocy liposomalnej cytarabiny podawanej dokanałowo.

PACJENCI I METODY Przeanalizowano dane 79 pacjentów (46 mężczyzn, 33 kobiety; mediana wieku: 48,5 roku [20–79]) z rozpoznaniem chłoniaka rozlanego z dużych komórek B (83,5% pacjentów) oraz pierwotnego chłoniaka śródpiersia z dużych komórek B (16,5%). Pacjentów leczono w klinikach hematologii w Krakowie oraz we Wrocławiu w latach 2009–2012. Wszyscy oni byli ocenieni jako pacjenci wysokiego ryzyka zajęcia OUN w przebiegu chłoniaka.

WYNIKI Reakcje uboczne zastosowania dokanałowego liposomalanej cytarabiny odnotowano u 59 pacjentów (74,7%), reakcje o dużym nasileniu wystąpiły w 7 przypadkach. Najczęściej zgłaszanym objawem był ból głowy (67,1%). Wynik w skali Karnofsky'ego w trakcie leczenia systemowego i stosowania profilaktyki uległ poprawie w 56 przypadkach (70,9%), u reszty badanych nie odnotowano zmiany. Mediana czasu obserwacji nie przekroczyła 28 miesięcy (1,4–52,1), w tym czasie nie osiągnięto mediany całkowitego przeżycia (*overall survival* – OS) ani mediany PFS (przewidywane OS i PFS po 48 miesiącach obserwacji to odpowiednio 86,1% i 90,1%).

WNIOSKI Uzyskane wyniki zachęcają do używania liposomalnej cytarabiny podawanej dokanałowo w ramach profilaktyki zajęcia OUN u pacjentów z chłoniakiem.

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