KU LEUVEN

FACULTY OF MEDICINE

Prevalence of leukoencephalopathy in cancer patients

Master Thesis proposed to achieve the degree of master in medicine by

Michiel MEYLAERS

Unit: Pediatric Hemato-Oncology

Department: Oncology

Promotor: Prof. Dr. UYTTEBROECK Anne

Mentor: PhD. SLEURS Charlotte

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COVER LETTER

Dear members of the Editorial board

We are proud to present our paper *"The prevalence of leukoencephalopathy in cancer patients".*

Given the increasing survival rates of cancer patients, aspects such as long-term side effects are attracting more attention in the literature. An important side effect of cancer treatment is neurotoxicity, which can affect brain development and long-term psychological functioning. It is important to recognize the development of leukoencephalopathy as a result of chemotherapy treatment. The diagnosis of leukoencephalopathy can exclusively be made with a magnetic resonance scan of the brain. The aim of this study is to give an overview of the prevalence of leukoencephalopathy in cancer patients based on a literature study.

As most studies were conducted in childhood acute lymphatic leukemia (ALL), there is little or no clear data of other cancers or cancer in adults. A clear overview was made of the role of the chosen chemotherapeuticals and their used dose or method of administration. As we will discuss, the timing of the magnetic resonance images also influences the prevalence.

Currently, there is little data available on the long-term effects on the structure of the brain and the neurocognitive outcome. In the future there will be a need for major follow-up studies to provide a clear picture. Meanwhile, other domains such as the influence of genetics need to be further investigated.

This study is an interesting review of the current literature and we believe it will make an important contribution to the current knowledge on leukoencephalopathy in cancer patients. This review took into account the type of chemotherapeutic drug, dose-related effects and the role of the timing of the MRI. Not only were studies with childhood ALL included, but the inclusion criteria also include other cancers. In addition, some studies with long-term follow-up were implemented.

With these statements in mind, we believe that our study is a good candidate for publication in your journal. We hope you share this opinion with us.

Finally, we declare that our study is an original, non-published work. We declare that there was no funding nor any conflicts of interest for this research. The study was approved by the Ethics Committee of University Hospitals Leuven, Belgium.

Yours sincerely

Michiel Meylaers

ABSTRACT

Introduction: Due to the increasing use of chemotherapy in cancer patients, various neurotoxic effects are described, of which leukoencephalopathy is the most common. Most reports contain a childhood acute lymphoblastic leukemia population, which are treated with high doses of methotrexate. Given the potential long-term effects and lack of overview of prevalences of acute leukoencephalopathy, we aimed to get a clear picture of the prevalence of leukoencephalopathy.

Methods: A comprehensive literature search was approved by using the PubMed/Medline database. The search strategy was based on various components, including “MRI”, “cancer”, “therapy” and “PRES”.

Results: The patient groups were divided according to their type of cancer, administered chemotherapeuticals, time of sampling of magnetic resonance images and follow-up scanning. If ALL patients were scanned on a regular basis, the prevalence was 27 % - 76 %, versus a prevalence of 26 % - 83 % if scanned after a central nervous system event. The results of the follow-up scans were very variable. A higher prevalence was observed in patient groups with higher doses of methotrexate (5 g/m^2 MTX, 42 % - 87 %) than in patients with lower doses (< 5 g/m^2, 32 % - 67 %). In breast cancer patients, no difference was found in prevalence of white matter lesions, however, there were more infratentorial microbleedings in the chemotherapy group. Additionally, in most studies patients had lower scores on neurocognitive tests or had more neurobehavioural problems. There were no data available of other cancers.

Conclusion: With the exception of childhood ALL studies, there is a lack of research concerning the prevalence in patients treated with other chemotherapeuticals, with other cancers and at all ages. Large, longitudinal and prospective follow-up studies will be necessary to determine long-term effects of leukoencephalopathy. Earlier identification using newer neuroimaging techniques and neurological biomarkers may allow healthcare professionals to define risk groups and to develop intervention techniques and preventive measures against central nerve system-related side effects.

NEDERLANDSTALIGE SAMENVATTING

Introductie: Door een toenemend gebruik van chemotherapie bij kankerpatiënten worden steeds meer en meer neurotoxische nevenwerkingen gerapporteerd, waarvan leukoencefalopathie de meest voorkomende is. De meeste studies hierrond werden verricht bij acute lymfoblastische leukemie bij kinderen, die werden behandeld met hoge dosissen methotrexaat (MTX). Gezien de mogelijke langetermijn effecten van de therapie en het ontbreken van een overzicht van de prevalenties van acute leukoencefalopathie, probeerden we met deze studie een duidelijk overzicht te maken van de prevalentie van leukoencefalopathie.

Methode: Er werd een strategische literatuurstudie uitgevoerd op basis van de PubMed/Medline database. De zoekstrategie werd gebaseerd op verschillende componenten, met als voornaamste zoektermen “MRI”, “kanker”, “therapie” en “*PRES*”.

Resultaten: De geïncludeerde patiënten werden opgedeeld volgens het type kanker, de toegediende chemotherapie, de timing van de magnetische resonantie scan (MRI) en eventuele opvolgscans. Wanneer ALL patiënten een MRI hersenen kregen op regelmatige basis, was de prevalentie 27 % - 76 %, terwijl er een prevalentie is van 26 % - 83 % wanneer de patiënten enkel werden gescand na een klinisch event van een centraal zenuwstelsel (bv. epilepsie-aanval, hoofdpijn, visusstoornissen enz.). De resultaten van de opvolgscans waren heel gevarieerd. In de patiëntengroep met hogere dosissen van MTX (5 g/m²) werd een grotere prevalentie leukoencefalopathie (42 % - 87 %) gevonden dan in de groep met lagere dossisen MTX (< 5 g/m^2, 32 % - 67 %). Bij borstkankerpatiënten vonden we geen verschil in de prevalentie van witte stof letsels, echter werden wel meer infratentoriële microbloedingen gezien bij patiënten die chemotherapie kregen. Daarnaast hadden patiënten met leukoencefalopathie in de meeste studies ook lagere scores op neurocognitieve en neurologisch gedrag. Er waren niet voldoende data beschikbaar over andere types van kanker.

Conclusie: Met uitzondering van ALL studies op kinderleeftijd, zijn er te weinig data beschikbaar over de prevalenties bij patiënten die behandeld worden met andere chemotherapeutica, met andere kankers of op andere leeftijden. In de toekomst zijn grotere, longitudinale en prospectieve studies nodig om langetermijn effecten van leukoencefalopathie te bepalen. Nieuwe technieken voor neurologische beeldvorming of opsoren van neurologische biomarkers moeten gezondheidsmedewerkers toelaten om risicogroepen te bepalen, goede interventietechnieken te ontwikkelen en preventieve maatregelen te nemen tegen nevenwerkingen in het centraal zenuwstel.

INTRODUCTION

As cancer treatments improve survival rates, long-term side effects and quality of life increasingly receive attention. As treatments not only affect the tumor, but also healthy tissue, toxic side effects can include acute cardiotoxicity, neurotoxicity, mucositis etc., which affects long-term life quality. As neurotoxicity might affect brain development and long-term psychological functioning, increasingly neuropsychological research has been conducted recently.[1] Cognitive impairment that could be observed after chemotherapy has a wide spectrum of clinical manifestations, ranging from very subtle to more severe, including memory, processing speed, attention being etc.[2]

The most frequent neurological complication after chemotherapy is the development of leukoencephalopathy, which is confirmed by magnetic resonance (MR) images. Leukoencephalopathy is an increasingly recognized complication due to easier access to MR imaging and increased intensities of chemotherapeutics. In the acute phase, this usually presents as the posterior reversible encephalopathy syndrome (PRES).[3,4] The most common clinical features of PRES are seizures with headache, altered mental status, neurological deterioration and/or visual impairment. Less frequently observed are dysarthria or hemiplegia.[4–6] Other acute neurological complications of the use of chemotherapy are stroke-like episodes, intracranial hemorrhages or cerebellar syndromes.[3,4]

MR imaging is essential for diagnosing leukoencephalopathy. Generally, transient lesions are T2-weighted hyperintense and localized in de subcortical white matter, predominantly in the posterior temporal, parietal and occipital areas. Furthermore, it may affect basal ganglia, cerebellar hemispheres and the brainstem. The diagnosis is usually based on conventional MR images. However, in some cases, diffusion-weighted MR is needed because of the high signal intensity in the deep white matter.[3] Moreover, diffusion-weighted MR helps to distinguish cytotoxic edema from vasogenic edema, which is the classic imaging abnormality of PRES and suggests a reversible process with favorable prognosis, in contrast to cytotoxic edema.[6] Ultimately, MR images are preferred for long-term follow-up in order to diagnose or monitor leukoencephalopathy.

In recent years, extensive research regarding development of leukoencephalopathy as a result of chemotherapy in cancer patients has been published. However, most data are reported in childhood Acute Lymphoblastic Leukemia (ALL) and few studies can be found in other cancer patient populations. In ALL patients, the different protocols always use methotrexate (MTX) in high doses, either intravenously (IV) or intrathecal (IT), and may be a possible causal factor in the development of encephalopathy.[10,11] In addition to the proven neurotoxicity of MTX, Sleurs et al. (2016) also reported neurotoxic effects of cytostatics such as alkylating substances (i.e. ifosfamide, cyclophosphamide, cisplatin) or vincristine.[10]

Beside the effect of chemotherapy, the cancer itself also has a negative influence on cognitive function. Explanations can be diagnosis-related emotional stress or DNA damage/deficiencies in DNA repair mechanisms. Furthermore, chemotherapeutic agents are associated with elevated cytokine release. Cytokines have important roles in normal CNS function, including neural repair, neural cell function and the metabolism of serotonin and dopamine, both of which are neurotransmitters for normal cognitive function. The relationship between cytokines and cognitive function is clearly an inverse association, especially for interferon-α and interleukin 2. Longitudinal studies have shown decrements in domains such as processing speed, executive functions, spatial ability and reaction time. Furthermore, cytokine levels are increased in cancer patients before treatment. This increase, in combination with triggering of cytokines in

response to DNA damage by the use of chemotherapy, may contribute to the development of posttreatment cognitive problems.[5,12]

Soussain et al. (2009) and Ahles et al. (2012) also demonstrated the relevance of polymorphisms of genetic factors. For example, patients who carried apolipoprotein E ε4 (APO E4) allele or who have a polymorphism of the methylene tetrahydrofolate reductase enzyme, causing increasing levels of methotrexate, scored poorly on visual memory and spatial ability tests. APO E4 is a complex glycolipoprotein involved in neural repair. The allele is associated with prominent cognitive dysfunction disorders, such as Alzheimer's disease, and poor outcomes in stroke, traumatic brain injury or cancer survival.[5,12]

The induced neurotoxicity can be acute or delayed, yet it remains uncertain whether observed abnormalities are completely reversible or not.[5] Schagen et al. (2002) concluded that there was an improvement in test performance four years after completion of treatment of breast cancer. However, they could not demonstrate any difference in cognitive functioning between patients treated with high-dose chemotherapy, various regimes of chemotherapy and patients who did not receive systemic therapy.[1]

Given the potential long-term effects of neurotoxicity in childhood ALL studies and lack of overview of prevalences of acute leukoencephalopathy, we aimed obtaining a clear picture of the prevalence of leukoencephalopathy due to the administration of chemotherapy as a cancer treatment, both in children and in adults in all types of cancer.

METHODS

Search strategy

A comprehensive literature search was performed by using the PubMed/Medline database. Publication date was restricted from 1995. No limit was applied for language and foreign papers were excluded. The search strategy was based on various components, including “MRI”, “cancer”, “therapy” and “PRES”. Each term was subdivided in different search terms: ‘MRI’ was divided into ‘MRI, T2-weighted MRI or FLAIR’. Cancer was divided into ‘cancer, tumor, leukemia or neoplasms’. ‘Therapy’ was divided into ‘chemotherapy or radiotherapy’. Finally, we searched for leukoencephalopathy with the terms ‘posterior reversible encephalopathy or leukoencephalopathy or cerebral ischemia or stroke’. Both studies in children and adults were accepted.

Study selection

Study selection was conducted at three different levels. First, potential articles were screened by their titles to exclude studies which did clearly not meet the inclusion conditions. Second, studies were selected by abstract and finally, if the abstract was eligible, studies were selected by full text. This systematic and thorough screening ensured the inclusion of the correct studies. It was supplemented by cited references from retrieved articles or other relevant articles.

Exclusion criteria were: (1) studies published before 1995 (although the restriction in de PubMed/Medline database), (2) studies with animals, (3) case reports with 4 or fewer cases (we selected a cut-off of minimal 5 included patients), (4) studies with patients who received cranial irradiation, (5) pharmacological studies which only aimed to study the effect of new products, (6) studies with patients who had no cancer or received another diagnosis, (7) studies with not MR images of interest (e.g., only T1-weighted), (8) studies in which patients did not receive chemotherapy and (9) studies with patients diagnosed with brain tumors. Because of the lack of limitations in language during the search strategy, foreign language became an additional exclusion criterion. Lastly, full text had to be available.

Thus, important inclusion criteria were (1) studies with adults and children, (2) studies which researched the prevalence of leukoencephalopathy, further defined as PRES, ischemia, demyelination, hyperintensities on MR images, white matter lesions or vascular damage, and (3) the use of T2-weighted or FLAIR MR images or, additionally, diffusion weighted MR.

RESULTS

The literature search on the PubMed/Medline database returned 967 articles which were systematically screened as described in the previous section. Seven additional articles were added, based on references from other included studies and one recent published article after completion of our database. The selection resulted in 41 articles (Figure 1). 19 studies retrospectively analyzed the prevalence of PRES or leukoencephalopathy in patients with cancer. As mentioned, most of our obtained data belong to childhood ALL studies.

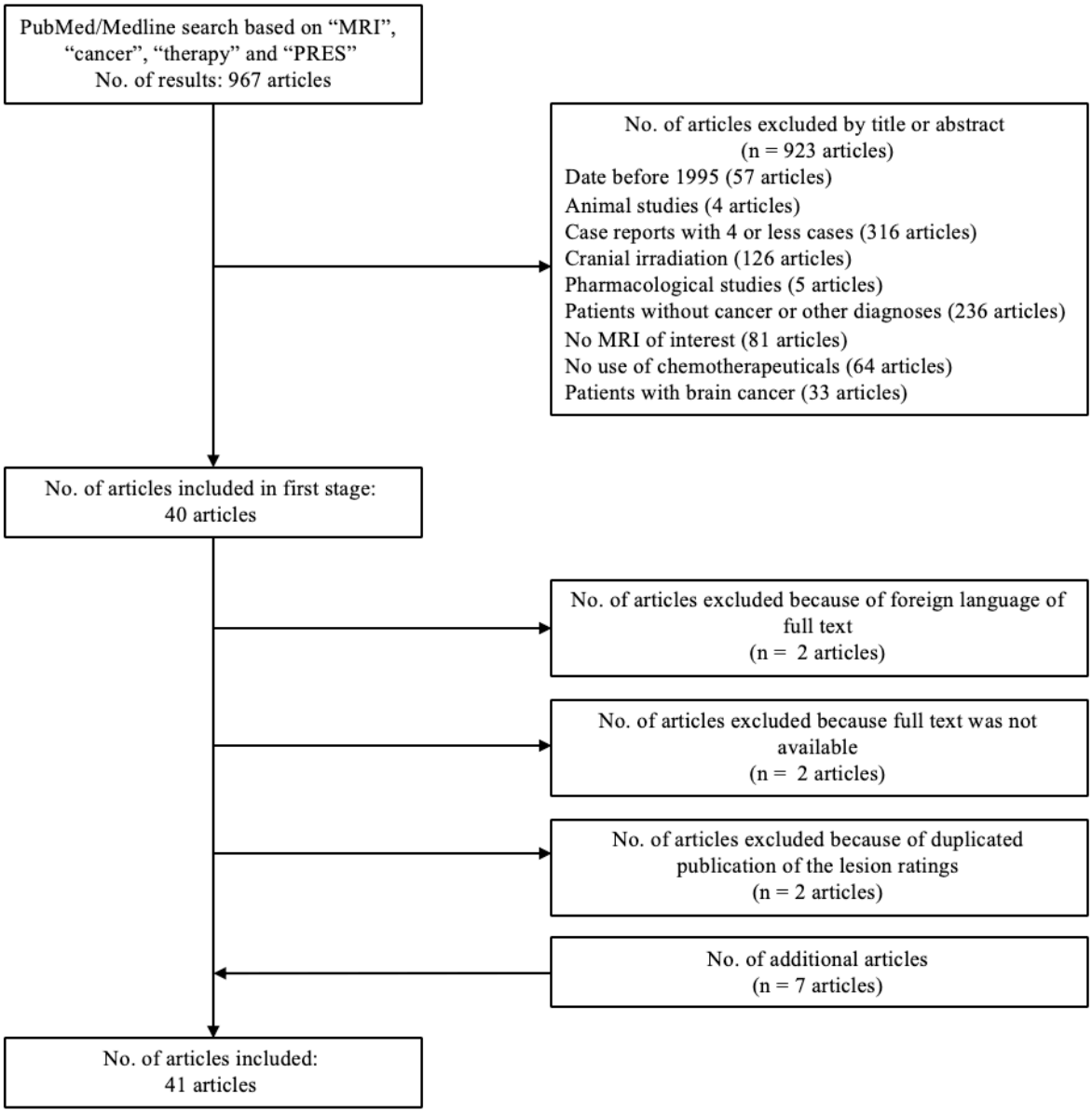

Figure 1. Flow diagram showing the selection process and exclusion criteria.

To analyze the prevalence of leukoencephalopathy, we searched for specific data or features such as type of cancer, age of patients, use of chemotherapeuticals, type and timing of MR

Table 1: Overview of included studies.

Autor (year)	Type cancer	Range of age (years)	Number of patients	Chemotherapeutical			Type of MR image	Time of MR image	Regions	Prevalence
				IT	HD-MTX	Other				
Baytan et al. (2015)	ALL	Children	323	TIT and mono MTX	5 g/m^2	PRED, VCR, DNR, L-ASP, cytarabine, CPM, IFO, DEXA, ETO	T2, FLAIR	- after CNS event	- Parietal, - Occipital areas.	26 % if CNS event, 2 % in total population
Bhojwani et al. (2014)	ALL	Children	369	TIT	2.5 g/m^2 (low risk) or 5 g/m^2 (high risk)	Oral MTX, DEXA, VCR, CPM or cytarabine	T1, T2, FLAIR, PD	- postinduction - week 1 after re-induction (cons.) - week 48 (after cont.) - week 120 (after cont.) - during or after CNS event	NA	23 %
Cheung et al. (2016)	Non-B-ALL (high risk)	8 – 18	156	TIT	2.5 g/m^2 (low risk) or 5 g/m^2 (standard or high risk)	DEXA, L-ASP, CPM, DNR, DXR, VCR, mercaptopurine	T2, FLAIR, DTI	- week 6-7 (ind.) - week 1 after re-ind. (cons.) - week 48 (after cont.) - week 120 (at end of therapy)	NA	27 % (from those, 78 % after 5 years)
Cheung et al. (2018)	ALL	Survivors of ALL at children's age	173	TIT	2.5 g/m^2 (low risk) or 5 g/m^2 (standard and high risk)	Oral MTX	T1, T2, FLAIR, DTI	NA	- frontal and occipital fasciculi - superior longitudinal fasciculi - corona radiata	30 % (from those, 79 % after 5 years)
Cole et al. (2009)	ALL	Children	36	TIT	/	MTX or aminopterine per os	T1, T2, FLAIR	45 days after therapy	Periventricular or subcortical white matter lesions	25 %
Duffner et al. (2014)	B-ALL	1 - 10	31	TIT and mono MTX	After IT [1a]	MP + oral MTX	T1, T2, FLAIR	NA	NA	68 % mild[2] 3 % moderate[2]
	B-ALL	1 – 10	23	TIT and mono MTX	Concurrent with IT [1b]	None				22 % mild[2]
Hertzberg et al. (1997)	ALL	6 at diagnosis	39	Mono MTX	2 g/m^2	NA	T2, PD	7 years after diagnosis	NA	38.5 %
Kingma et al. (2001)	ALL	< 7 years at diagnosis	16	Mono MTX + prednisolone	2 g/m^2	Oral MTX, cytarabine arabinoside	NA	10 years after diagnosis	NA	38 % (50 % definitely abnormal, 50 % probably abnormal)
Krull et al. (2012)	Hodgkin lymphoma	18 - 55 (<18 at time of diagnosis)	62	/	/	Doxorubicin and/or anthracyclines and/or bleomycin	T1, T2, FLAIR, PD	> 15 year after diagnosis	- Frontal - Parietal - Semioval nucleus	- 35 % frontal - 13 % parietal - 30 % semioval nucleus
Lim et al. (2011)	ALL, AML, CML, NHL, solid tumors	4 – 14	12	NA	NA	NA	FLAIR	- after CNS event	White matter: - frontal - parietal - temporal - occipital	50 %
Mahoney et al. (1998)	B-ALL	Children	1218	1x TIT 12x IT MTX		VCR, L-ASP, prednisolone	T2	- after CNS event	NA	79 % if CNS event, 6 % in total population
				Regimen A:	1 g/m^2	IM MTX, 6-MP				75 % if CNS event
				Regimen B:	/	Oral MTX + IM MTX, 6-MP				15 % if CNS event
				Regimen C:	1 g/m^2	IM MTX, 6-MP (dose less than regimen A)				77 % if CNS event

Nassar et al. (2017)	ALL	Children	498	TIT	2.5 g/m² (low risk) or 5 g/m² (standard and high risk)	MTX, mercaptopurine, VCR, DEXA	T1, T2, FLAIR	- week 5 after ind. - week 7 after cons. - week 120 at end of therapy	NA	- week 5: no diff. - week 7: 56 % vs. 13 % - week 120: 39 % vs. 6 %
Parasole et al. (2010)	ALL	Children	253	Mono MTX	None, 2 g/m² or 5 g/m²	DEXA, VCR, DNR, L-ASP, VDS, IFO, 6-MP	T1, T2, FLAIR	- at time of CNS event - 6 months after event	- Frontal, - Parietal, - Occipital, - Hippocampal-, - Semioval nucleus areas	37 % if CNS event, 4 % in total population (from those, 36 % after 6 months)
Reddick et al. (2005)	ALL	1 – 19	45	TIT	2.5 g/m² or 5 g/m²	/	T1, T2, FLAIR	Week 6, 7, 31 and 120 after start	NA	76 % (87 % in high risk, 67% in low risk)[3]
Rollins et al. (2004)	B-ALL	12 – 15	194	Mono MTX	After IT (IV MTX)	DEXA, VCR, L-ASP, DNR, 6-MP, Ara-C, CPM and/or oral MTX	T1, T2, FLAIR, ADC map	Within 17 – 23 hours after CNS event	- Cerebral atrophy and callosal splenium - Frontal and parietal lobe	83 % if CNS event, 3 % in total population (from those, 20 % after 36 months)
Suzuki et al. (2014)	AML	0 – 16	36	NA	NA	Cytarabine, ETO, mitoxantrone	T2, FLAIR	NA	NA	4 %
	ALL		108	/	2 g/m² or 5 g/m²	Oral MTX, DEXA, VCR, 6-MP				
	NHL		15	NA	NA	Steroids, VCR, CPM, THP-adriamycin, L-ASP, actinomycin D, MTX, cytarabine				
	HL		2	NA	NA					
Tsujimoto et al. (2016)	ALL	0 – 15	25	TIT	< 5 g/m²	Oral MTX	T1, T2, FLAIR	Before start of therapy and at time of CNS event	NA	32%
	ALL	0 – 15	31	TIT	5 g/m²	/				42 %
Ziereisen et al. (2006)	ALL or NHL	Children	90	TIT or mono MTX	5 g/m²	VCR, PRED or DEXA, DNR, L-ASP, CMP, Ara-C, 6-MP or 6-TG	T1, T2, FLAIR, ADC map (6 patients)	- after therapy - after relapse - after CNS event	- frontal - parietal - occipital - supratentorial ctx - cerebellar ctx - thalamus	17 % (0 % after 1 – 7 months)
Koppelmans et al. (2015)	Breast cancer	50 – 80 (survivors)	187	/	/	CMP, oral MTX and 5-FU	T1, T2 GRE, FLAIR	NA	NA	No difference in: - white matter lesions - cortical or lacunar infarctions - lobar microbleeds. More infratentorial microbleeds.

ADC: apparent diffusion coefficient; ALL: acute lymphoblastic lymphoma; Ara-C: cytocine arabinoside; B-ALL: B-lymphocyte ALL; cons.: consolidation; cont.: continuation; CNS: central nerve system; CPM: cyclophosphamide; ctx: cortex; DEXA: dexamethasone; diff. difference; DNR: daunorubicin; DTI: diffusion tensor imaging; ETO: etoposide; FLAIR: fluid attenuated inversion recovery; HD-MTX: High-dose methotrexate (> 0,5 g/m²); HL: Hodgkin lymphoma; IFO: ifosfamide; ind.: induction; IM: intramuscular; IT: Intrathecal; L-ASP: L-asparaginase; MP: mercaptopurine; MR: magnetic resonance; MTX: methotrexate; NA: not available; NHL: Non-Hodgkin lymphoma; PD: proton density weighted sequence; PRED: prednisolone; T-ALL: T-lymphocyte ALL; TIT: triple intrathecal therapy with MTX, cytarabine and prednisolone; T2 GRE: T2-weighted gradient recalled echo accelerated MR images; VCR: vincristine; VDS: vindesine; 5-FU: 5-fluorouracil; 6-MP: 6-mercaptopurine; 6-TG: 6-thioguanine

[1] 1a: children received standard MTX (20 mg/m² IM) weekly, 1b: received divided dose MTX (25 mg/m² PO Q 6 hours X 4 every other week)

[2] Mild: mild diffuse T2 hyperintensities in the periventricular white matter/centrum semiovale); Moderate: moderate T2 hyperintensities involving confluent deep white matter from the frontal horns to the trigone, which may extend to the subcortical U-fibers.

[3] Low risk: patients in which the plasma steady-state concentration of MTX was 33 μmol/L; High risk: patients in which the plasma steady-state concentration of MTX was 65 μmol/L.

images, regions of radiologic findings suggesting leukoencephalopathy and, of course, the prevalence of leukoencephalopathy or PRES detected. As all ALL patients receive high doses of MTX (HD-MTX), this will be the most commonly used chemotherapy. It nevertheless remains important to know which other products were administered. Based on these requirements, an overview was made of the relevant articles (Table 1).

Prevalence of leukoencephalopathy

Leukemia patients

Many studies described the prevalence of leukoencephalopathy in patients diagnosed with leukemia.[4,11,13–28] The age of included patients varied from one to nineteen years old, no data were found for adult ALL. All patients received MTX, IT and IV (only two studies did not describe exact the used protocol[4,15]). Depending on different chemotherapy protocols, the children received either monotherapy with IT MTX or, more recently, triple intrathecal therapy (TIT), which consist of a combination of MTX, cytarabine and prednisolone.

The dose of HD-MTX varied between 2 g/m^2 and 5 g/m^2. Only Mahoney et al. (1998) used a protocol with 1 g/m^2 MTX in some regimes.[20] Some studies divide the patient groups based on the risk of central nerve system (CNS) expansion into low-risk patients, standard-risk patients and high-risk patients, with respectively 2 g/m^2 or 2.5 g/m^2 MTX for low-risk patients and 5 g/m^2 MTX for patients in standard- or high-risk groups.[13,15,22–24,27,28] Additional therapy varied according to the guidelines of the protocol used. Most frequently administered drugs were oral corticosteroids, MTX, vincristine, L-asparaginase, daunorubicin, cyclophosphamide and 6-mercaptopurine.

There is a wide variation regarding the data used to calculate the prevalence of leukoencephalopathy. Some studies scheduled imaging of the brain on a regular basis, for example after induction, re-induction, consolidation or at end of therapy. The prevalence in this patient group ranged from 27 % to 76 %.[13,14,23,24,27] Cheung et al. (2016, 2018) reported positive MR images in 78 % to 79 % 5 years after diagnosis of leukoencephalopathy.[23,24] Two studies performed long-term MR imaging follow-up of ALL patients at 7 or 10 years after diagnosis and showed a prevalence of 38 %.[18,19] A second group of patients were only scanned during therapy at time of a CNS event, i.e., an epileptic seizure, visual disturbances, headache, aphasia, changed behavior, headache, etc. The prevalence for this group was 26 % to 83 %.[4,11,16,20,21] Some studies only included patients after they were scanned based on their clinical presentation of PRES and thus had a prevalence of 100 % (an overview was made in Table 2).[29–34] When this patient group received a follow-up MR image, the prevalence was 49 % after 8 weeks,[31] and 20 % after 0.5 – 36 months.[11,34] A third population of patients, screened on a regular basis and after a CNS event, showed leukoencephalopathy in 17 % to 37 %.[17,22,28] In one study, no patients showed lesions on MR images 1 – 7 months after therapy.[17] Another study reported a prevalence of 36 % after 6 months after the CNS event.[28]

Two studies divided their patient population in different subgroups, i.e., the low-risk group which received IV MTX at a dose of less than 5 g/m^2 versus the standard- and high-risk group which had 5 g/m^2 IV MTX. Patients in the standard- and high-risk groups had a higher prevalence of leukoencephalopathy (42 % to 87 %) than patients in the group with a lower dose of IV-MTX (32 % to 67 %).[13,16] Cheung et al. (2016) studies the cumulative dosages of

Table 2: Overview of included articles with a 100 % prevalence of leukoencephalopathy or PRES.

Autor (year)	Type cancer	Range of age (years)	Number of patients	Chemotherapeutical			Type of MR image	Time of MR image	Regions	Prevalence
				IT	HD-MTX	Other				
Baehring et al. (2008)	ALL or large cell lymphoma	6 – 20	19	Mono MTX	NA	NA	T2, FLAIR, DWI, ADC map	NA	NA	100 %
	Breast cancer	40 – 52	4	NA	NA	Capecitabine				
	Cancer of (sigmoid-)colon, nasopharynx, pancreas	23 – 61	4	NA	NA	Capecitabine, 5-FU, carmofur,				
Belarami et al. (2011)	ALL	4 – 11	4	NA	NA	MTX, DEXA, DXR, VCR, L-ASP, cytarabine	NA	Within 1 week after event	NA	100 %
	Pituitary germ cell tumor	7	1	/	/	BEP				
Carson et al. (2014)	HL	47 – 51	3	/	/	BV, DXR, bleomycin, vinblastine, dacarbazine, IFO, carboplatine, ETO, methyl-PRED, cytarabine, cisplatin	NA	NA	NA	100 %
	Primary cutaneous anaplastic large cell lymphoma	38	1	/	/	BV, topical CS, MTX, bexarotene, IFN-α, vorinostat				
	Transformed mycosis fungoides	72	1	/	/	BV, topical CS, phototherapy, IFN-α, bexarotene, localized RT				
Choi et al. (2001)	Breast cancer	33 – 57	6	/	/	5-FU, CPM, epirubicin, carmofur	T1, T2	NA	NA	100 %
Fitzgerald et al. (2014)	MM	51 – 75	12	/	/	Bortezomib, DXR, thalidomide, carmustine, ETO, cytarabine, melphalan, cisplatin, (tem)sirolimus, DEXA, rituximab, adriamycin, carfilzomib or CPM	NA	NA	NA	100 %
	Other solid tumors	33 – 67	8	/	/	Wide range of different chemotherapeuticals				
Kamiya-Matsuoka et al. (2016)	Leukemia and others	31 - 74	69	NA	NA	Tacrolimus, DXR, VCR, DEXA, different monoclonal antibodies	T1, T2, FLAIR, DWI, ADC map	NA	Most in: - parietal & occipital lobes Less in: - frontal & temporal lobes - cerebellum - brainstem - thalami & basal ganglia - corpus callosum	100 % (49 % after 8 weeks)

Kamiya-Matsuoka et al. (2017)	47,8 % primary hematological, 52,2 % solid tumor	30 – 70 (at diagnosis)	46	/	/	CPM, VCR, DXR (most used)	T1, T2, FLAIR, DWI, ADC map	NA	NA	100 %
Li et al. (2015)	ALL, lymphoma	3 – 12	8	NA	Na	NA	T1, T2	NA	- parietal - occipital - frontal - temporal regions or combinations	100 % (20 % after 2 weeks)
Lucchini et al. (2008)	ALL	2 – 14	9	NA	NA	NA	T2, FLAIR	At time of CNS event (within 24 hours)	(Sub)cortical in - occipital, - frontal, - parietal, - temporal areas.	100 %
Tang et al. (2016)	ALL	5 – 14	11	NA	NA	MTX, cytarabine, DNR, VCR, L-ASP, prednisolone	T1, T2, FLAIR	0, 1, 3, 6 and 12 months	- parietal & occipital lobe - less in frontal & temporal lobe, cerebellum, semiovale nucleus and periventricular area	100 %

ALL: acute lymphoblastic lymphoma; Ara-C: cytocine arabinoside; B-ALL: B-lymphocyte ALL; BEP: triple chemotherapy with bleomycin, etoposide and cisplatin; BV: brentuximab vedotin (monoclonal antibody targeting CD30-positive cells); CNS: central nerve system; CPM: cyclophosphamide; ctx: cortex; CS: corticosteroids; DEXA: dexamethasone; DNR: daunorubicin; DWI: diffusion weighted imaging; DXR: doxorubicin; ETO: etoposide; FLAIR: fluid attenuated inversion recovery; HD-MTX: High-dose methotrexate (> 0,5 g/m²); IFN-α: interferon alpha; IFO: ifosfamide; IT: Intrathecal; L-ASP: L-asparaginase; MM: multiple myeloma; MP: mercaptopurine; MR: magnetic resonance; MTX: methotrexate; NA: not available; NHL: Non-Hodgkin lymphoma; PD: proton density weighted sequence; PRED: prednisolone; RT: radiotherapy; T-ALL: T-lymphocyte ALL; TIT: triple intrathecal therapy; T2 GRE: T2-weighted gradient recalled echo accelerated MR images; VCR: vincristine; VDS: vindesine; 5-FU: 5-fluorouracil; 6-MP: 6-mercaptopurine; 6-TG: 6-thioguanine

neurotoxic agents between patients with or without persistent leukoencephalopathy and found no statistical differences.[23] However, Reddick et al. (2005) concluded that higher doses and more courses of IV MTX placed patients at higher risk for leukoencephalopathy.[13] No difference can be found between patients who got TIT therapy versus patients with monotherapy with IT-MTX (37 % to 83 % if mono MTX and after CNS event versus 22 % to 76 % if TIT).[4,11,13,16–19,21–28] Only Mahoney et al. (1998) showed a significantly higher prevalence of leukoencephalopathy in patients with TIT versus mono IT MTX. [20] Only Cheung et al. (2016) found no significant difference in the cumulative dosages of neurotoxic agents between patients with or without persistent leukoencephalopathy.[23]

Bhojwani et al. (2014) revealed in an univariate analyses that patients age older than 10 years were at higher risk for neurotoxic events than patients with age 1 to 10 years.[22]

Concerning the regions of the brain with white matter lesions were found on MR images, most studies seem to report roughly the same results. Especially the frontal, parietal and occipital regions were affected by encephalopathy.[4,11,17,21,28,32–34] This correlates to the most common symptoms of the patients: epileptic seizures or visual disturbances. They also found white matter lesions in the temporal lobe, semioval nucleus, hippocampus and the thalamus.[4,17,21,28] Lesions in the fasciculi or corona radiatia,[23] in the callosal splenium,[11] or in the cerebellum[17] were respectively each in one study reported.

Breast cancer survivors

Koppelmans et al. (2015) described the prevalence of leukoencephalopathy in breast cancer survivors. Patients age was between 50 and 80 years old and they received a combination of cyclophosphamide, 5-fluoruoracil, and oral MTX. With the exception of infratentorial microbleedings, no difference was found between patients who received adjuvant chemotherapy versus a population-based reference group in white matter lesions, cortical or lacunar infarctions or lobar microbleedings. However, patients receiving chemotherapy had lower cognitive performance.[35]

Other cancers

Merely four studies included patients with other cancers than ALL or breast cancer.[4,15,17,36]

Two of them included patients with Hodgkin lymphoma at childhood.[15,36] The given chemotherapeuticals were different in both studies. However, Krull et al. (2012) performed MR images more than 15 years after diagnosis, at an age between 18 and 55 years. The prevalence of leukoencephalopathy was 35 % in the frontal lobe, 13 % in the parietal lobe and 30 % in the semioval nucleus.[36]

Non-Hodgkin lymphoma (NHL) at childhood was described in three studies, but none of them made any distinction in used chemotherapeuticals, regions in which the white matter lesions were most visible on MR image or calculation of the prevalence of leukoencephalopathy and are therefore not valuable in this discussion.[4,15,17] Suzuki et al. (2014) described a childhood population with ALL, acute myeloid leukemia (AML), Hodgkin lymphoma and NHL with a prevalence of 4 % (only ALL patients).[15]

Lim et al. (2011) evaluated MR images after a CNS event in chronic myeloid leukemia (CML), NHL and solid tumors such as osteosarcomas, germ cell tumors and rhabdomyosarcoma. No

data of the given chemotherapeuticals were available. In 50 % of the patients, MR images were positive for white matter compatible with PRES. Wernicke encephalopathy was the second most common encephalopathy (25 %).[4]

Neurocognitive outcome of leukoencephalopathy

Only a few studies discussed the neurocognitive outcome of patients with leukoencephalopathy. As mentioned earlier, some authors included protocols with follow-up MR images of the brain in order to make some statements about the reversibility of PRES.

Since leukoencephalopathy affects white matter, we can expect a change in the neurocognitive domain. Some authors have tried to make a clear statement of these neurocognitive abnormalities, however, it is difficult to compare the studies since they all have their own tools, questionnaires or indices for the assessment of the neurocognitive outcomes.[18,23,24,26,27,35,36]

Most studies conclude that patients had lower scores on neurocognitive tests or had more neurobehavioural problems. Neurocognitive outcome was mostly evaluated by measures of the intelligence quotient (IQ). Neurobehavioural problems included problems with working memory; initiation, planning and organizing; memory span; executive functions and processing speed.[18,23,24,26,27,35,36]

Two studies found no significant association found between neurocognitive performance measures and the presence of leukoencephalopathy.[24,26] Though according to Duffner et al. (2014), survivors of leukoencephalopathy composed 88 % of patients with a score more than one standard deviation (>1 SD) below the mean full-scale intelligence. They also approved a strong relationship between the MR images and neurocognitive outcome: the majority (75 % - 100 %) of the children with ALL treated with HD-MTX who scored >1 SD worse than the normative mean also had leukoencephalopathy.[26] Other authors reported a clear cognitive decline in patients with leukoencephalopathy.[18,24,26,27,35]

Looking at the neurobehavioural problems, all studies reported more problems in patients with leukoencephalopathy.[18,23,24,27,36] Two studies included patient-reported problems below population norms.[23,36] Especially the white matter integrity in the frontostriatal tract is associated with neurobehavioural outcome, which is integral to executive functions, than with global frontal or parietal lobes.[23,24]

DISCUSSION

Leukoencephalopathy is a well-known neurological side effect of chemotherapy. Because ALL is the major part of pediatric oncology, most studies are performed in childhood ALL. We conclude that there is a large variation of prevalence of leukoencephalopathy (approximately 25 % - 80 %) with or without a CNS event. Additionally, there is a marked difference in prevalence between studies with a regular scheme for scanning the brain versus studies in which patients were only scanned after a CNS event. It is not surprising that the prevalence is higher after a CNS event. In order to compare the prevalence in both groups (i.e., the group with systematic screening versus the group with MR scan after a CNS event), the result of the group with a scan after a CNS event was plotted against the entire population. We found a much lower prevalence in the total population of this group (2 % to 6 %) compared to a systematic screening of the population (27 % to 76 %).

Looking at the risk factors of leukoencephalopathy, an older age at treatment seemed to be a risk factor although no reports of (young) adult ALL patients are found. In most of these studies, IV and IT MTX is considered as the most important risk factor. Some authors reported higher rates of leukoencephalopathy in ALL patients who were treated more frequently and more intensive with IV or TIT chemotherapy than patients with less intensive administration and leucovorin rescue.[13,16,20,24,26] Cole et al. (2009) did not use HD-MTX in their protocol and therefore reported a lower prevalence of leukoencephalopathy.[25] Other authors did not observe this treatment-related prevalence, which can be attributed to a threshold effect, such that beyond a specific level of dose intensity, the effect of the treatment on neurological outcomes is equal.[23] Besides dose-related interaction, the interaction between treatment drugs and psychological responses to the treatment (eg., biomarkers of oxidative stress and inflammation) might also define the severity of white matter changes.[23]

Chemotherapy is not only an important contributing factor to the development of leukoencephalopathy, several studies also describe a possible influence of arterial hypertension, although it is not clear whether this is a causal factor or a consequence of brain lesions.[4,6,9] It needs to be stressed that a the rise in blood pressure is not obligatory for the development of PRES.[4]

Looking at the neurocognitive outcome of patients with leukoencephalopathy, we can conclude that patients had lower scores on neurocognitive tests or had more neurobehavioural problems. Most reported are problems with working memory; initiation, planning and organizing; memory span; executive functions and processing speed.[18,23,24,26,27,35,36] However only one report described a cleared association between higher exposures to HD-MTX and executive function in long-term survivors.[23] The frequent use of corticosteroids may possibly be a contributing factor in the development of neurobehavioural disorders.[18]

Besides childhood ALL, only in breast cancer-related literature large studies concerning neuroimaging and neurocognitive outcome are found. Koppelmans et al. (2015) reported a lower than expected cognitive performance or cognitive decline in association with adjuvant chemotherapy in breast cancer survivors.[35]

Other types of cancer treated with intensive chemotherapy regimens, i.e., bone tumors, soft tissue tumors, Hodgkin and non-Hodgkin patients, in children as well as in adults are not investigated. Leukoencephalopathy can be a major side effect in these patients, since they also are treated with HD-MTX IV or other cytostatics, such as alkylating agents, vincristine or cisplatin.

Another important consideration is the discordance between symptoms (acute or long-term) and neuroimaging. According to Parasole et al. (2010), PRES will persist in about 10% of patients, with potentially severe or even fatal neurological disorders.[28] A number of patients however will still have persistent symptoms despite normal radiological findings. Therefore, a prolonged follow-up time of at least 2 years is recommended. Conversely, some cases have been described in which patients did not have any complaints despite positive MR images.[11,28]

As far as diagnostic tools are concerned, MR images have a fundamental role in the diagnosis and follow-up of leukoencephalopathy in cancer patients. MR imaging is able to distinguish between white matter lesions versus haemorrhagic accidents. CT scan is suboptimal for evaluating neurological events, except for vascular lesions.[28] In addition to MR imaging, newer techniques, such as diffusion tensor imaging (DTI), will be used more often. These newer techniques give better insights into the development and follow-up of brain damage. There is an association between DTI parameters of white matter and leukoencephalopathy which suggests that white matter integrity is negatively impacted during the early course of chemotherapy treatment. Investigators found associations between abnormal DTI parameters and deficits in neurocognitive performance in survivors of ALL treated with chemotherapy.[24] MR imaging of the brain will not be sensitive enough in future to explain relevant neurocognitive or neurobehavioural effects of cancer treatment, imaging techniques such as functional MR imaging, DTI, single photon emission tomography, MR spectography or positron emission tomography may provide new opportunities to understand changes in brain functioning.[18]

In addition to newer neuroimaging techniques, new biomarkers will play an important role in the future. Firstly, there may be a depletion of folate in CNS fluid after administration of MTX (both monotherapy and TIT), resulting in an accumulation of phosphorylated tau protein in CNS fluid and an increase of homocysteine in peripheral blood due to decreased remethylation.[20,25] Secondly, neuroinflammation caused by cytokine and interleukin production may cause vascular damage with vasogenic edema, promoting the development of white matter lesions.[15] Thirdly, diagnosis-related emotional stress can have a negative influence on the development of leukoencephalopathy and the cognitive problems.[5,12] Lastly, the detection of polymorphisms in genes responsible for neurogenesis will help clinicians in future to predict patient's susceptibility to leukoencephalopathy.[22]

The combination of newer neuroimaging techniques, detection of biomarkers, identification of genes involving neurogenesis or neuronal plasticity and a universal cognitive testing scale should provide more clarity in future about the long-term follow-up of leukoencephalopathy in cancer patients.

Limitations to our study include the great variability in leukoencephalopathy grades used by the different authors. Hereby it’s impossible to try to standardize the definition or grade of leukoencephalopathy. Secondly, most data concerned childhood ALL. Little or no data are available of adult ALL, other used chemotherapeuticals in leukemia patients or other cancers at all ages. However, because of the large group of ALL patients included in this study, the treatment is broadly uniform allowing fair comparisons. Studies with other cancers have very different numbers of patients, smaller homogeneous groups and different treatments. Making a clear statement with all these variables is not possible.

In the future, longitudinal follow-up studies will be necessary to determine whether the white matter lesions are permanent and will have a lasting effect on the functional outcome. Earlier identification of patients at risk may allow healthcare professionals to develop preventive measures against CNS-related side effects.

CONCLUSION

With the exception of childhood ALL studies, there is a lack of research concerning the prevalence in patients treated with other chemotherapeuticals, cancers and ages. Large, longitudinal and prospective follow-up studies will be necessary to determine long-term effects of leukoencephalopathy. Earlier identification using newer neuroimaging techniques and neurological biomarkers may allow healthcare professionals to define risk groups and to develop intervention techniques and preventive measures against CNS-related side effects.

CONFLICT OF INTEREST

None.

ROLE OF FUNDING STORE

None.

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