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The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomised study☆

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Abstract

To assess the benefit of intraventricular chemotherapy, patients with leptomeningeal metastasis (LM) from breast cancer were randomised to treatment including intraventricular (IT) chemotherapy ($n = 17$) or to non-intrathecal (non-IT) treatment ($n = 18$). Appropriate systemic therapy and involved field radiation therapy (RT) were given in both arms. Intention-to-treat analysis showed neurological improvement or stabilisation in 59% of the IT and in 67% of the non-IT group, with median time to progression of 23 weeks (IT) and 24 weeks (non-IT). Median survival of IT patients was 18.3 weeks and 30.3 weeks for non-IT patients (difference 12.9 weeks; 95% Confidence Interval (CI) −5.5 to +34.3 weeks; $P = 0.32$). Neurological complications of treatment occurred in 47% (IT) vs 6% (non-IT) ($P = 0.0072$). In conclusion, standard systemic chemotherapy with involved field RT for LM from breast cancer is feasible. Addition of intraventricular chemotherapy does not lead to survival benefit or improved neurological response, and is associated with an increased risk of neurotoxicity.

Keywords: Leptomeningeal metastasis; Neoplastic meningitis; Breast cancer; Intrathecal chemotherapy; Systemic treatment

1. Introduction

Leptomeningeal metastasis (LM) causes serious morbidity and without specific treatment presumably leads to death within 4–6 weeks [1–3]. Standard treatment consists of intraventricular administration of Methotrexate (MTX) in combination with involved field radiotherapy (RT). Promising results of such intensive treatment with responses in more than half of the patients and a median overall survival of 6 or 7 months have been observed in patients with LM from breast cancer [2,4]. However, lower response rates and a median survival of only 1–4 months were seen in more recent studies, with most patients dying of progressive leptomeningeal disease [5–11]. Additionally, intraventricular (IT) treatment is associated with neurotoxic side-effects [8,12,13].

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In a previous study, we observed neurological improvement and prolonged survival in some patients with LM from breast cancer who had been treated without IT chemotherapy. Outcome appeared to be more dependent on patient- and disease-related characteristics than on the intensity of treatment [8]. Presently, the role of intensive treatment in the management of LM from breast cancer is unclear, as there are no controlled studies comparing IT therapy with non-IT treatment.

We therefore designed a multicentre study to evaluate, in a randomised design, the efficacy of IT for breast cancer patients with LM. Aims of the study were to assess neurological response, survival and cause of death, and the toxicity of treatment.

2. Patients and methods

Patients with LM from breast cancer, who met the eligibility criteria and gave their informed consent, were stratified according to prognostic factors and randomised to receive either

1. intraventricular MTX, appropriate systemic therapy and, if necessary, RT to clinically relevant sites, or
2. appropriate systemic therapy and, if necessary, RT to clinically relevant sites, but without intrathecal chemotherapy.

2.1. Selection of patients

Patients younger than 75 years of age with LM from breast cancer and with a life expectancy based on systemic disease status of at least 3 months were eligible. The diagnosis of LM was based on clinical characteristics of LM, confirmed by tumour-positive cerebro-spinal fluid (CSF) cytology or, in absence of definite tumour positive cytology on abnormalities in the compound of CSF (protein >0.5 g/l, or lactate dehydrogenase (LDH) >26 U/l, or glucose <2.5 mmol/l, or cell count >5/mm^3) combined with characteristic findings on magnetic resonance scan (MRI) [14]. Adequate haematological function (white blood cells (WBC) count $>3 \times 10^9$ cells/l, platelet count $>100 \times 10^9$ cells/l) was required. Patients could only be included, if the prognostic index (PI) could be determined as > or <3.6. In a previous analysis of breast cancer patients with LM, a PI sumscore >3.6 predicted a median survival based on disease status including neurological disease of only 3 weeks [8]. (PI is the sum of age >55 years + 1.3; lung metastasis + 1.2; cranial nerve involvement + 1.5; lumbar CSF protein 0.51–1.0 g/l + 2; lumbar CSF glucose <2.5 mmol/l + 1.0). Patients were excluded in cases of progressive or untreated brain parenchymal metastasis. Small lesions (maximum diameter <15 mm) in continuity with the subarachnoid space were not a reason for exclusion.

2.2. Study design

Patients were stratified by institute and according to the PI (<3.6 versus >3.6), and randomised centrally by computer (Comprehensive Cancer Center Amsterdam) for intraventricular chemotherapy (IT group) or non-intrathecal treatment (non-IT group).

2.2.1. IT group

Within 2 weeks after randomisation, an Ommaya reservoir was inserted in the right lateral ventricle. MTX was diluted in 4 ml of sterile preservative-free saline and administered intraventricularly according to the following scheme: 10 mg of MTX twice weekly until the disappearance of tumour cells from 4 consecutive ventricular CSF samples, subsequently 10 mg of MTX once every 4 weeks for 3 months, 10 mg of MTX once every 6 weeks for 3 months, and 10 mg of MTX once every 4 months. In case of CSF relapse, again 10 mg of MTX was administered according to the same treatment scheme. In patients with initial tumour-negative ventricular CSF, the schedule started with 4 times 10 mg of MTX twice weekly. Blood analysis for WBC and platelets was performed at least once a week. When WBC or platelets decreased during MTX treatment, 15 mg of leucovorin was given orally, once every 12 h for 3 days. MTX was withheld if WBC fell below 3×10^9 cells/l or platelets below 100×10^9 cells/l. If clinical and MRI signs of leucoencephalopathy occurred MTX was replaced by Ara-C 40 mg intraventricularly administered according to the MTX schedule. If the patient failed to show a response after 4 weeks of treatment with MTX, it was advised to replace MTX by Ara-C 40 mg according to the MTX schedule. Because systemic treatment is assumed to be effective against LM, it was recommended to start systemic treatment concurrently with intraventricular chemotherapy. The choice of systemic treatment depended on previously given treatment, hormone receptor status and the condition of the patient. When the patient already receives systemic therapy it was at the discretion of the responsible physician as to whether the treatment would remain unchanged or be replaced by other systemic therapy, alike changes in treatment in case of progressive systemic disease. RT was delivered to sites of clinical relevance. Whole brain (WB) RT was applied at a dose of 30 Gray in 10 fractions.

2.2.2. Non-IT group

Choice for systemic treatment and RT were similar to the IT-group. Patients who were likely to have become resistant to systemic treatment or could not tolerate chemotherapy were treated with RT alone.

2.3. Evaluation of response and toxicity

Physical and formal neurological examinations, including assessment of neurotoxicity, were performed at diagnosis and every 2 weeks during the first 2 months and monthly thereafter until neurological progressive disease or death. During follow-up, response was recorded as remission, stable disease or progression.

Remission: distinct neurological improvement of at least one symptom or sign without deterioration of other neurological symptoms/signs. Stable disease: no distinct change of existing neurological symptoms/signs. Progression: deterioration of symptoms/signs or appearance of new neurological symptoms/signs of LM.

Time to neurological progression was defined as time from neurological stabilisation or response until neurological progression. Survival was defined as time from randomisation until death.

For the assessment of neurotoxicity, all events including appearance of signs which were not clearly related to LM were recorded. Leucoencephalopathy was evaluated according to a neurotoxicity scoring list specific for signs of subcortical dementia and including cognitive functioning, vigilance and gait disturbances. The items were scored as normal, moderately impaired or seriously impaired. To establish the diagnosis, MRI should show characteristic T2 hyperintensity involving the periventricular white matter.

Neuroimaging was not used to evaluate response of the neurological disease itself.

2.4. Statistical analysis

Overall survival from randomisation was the primary endpoint. The original design was to test the null hypothesis of equal survival in both groups against the one-sided alternative that the non-IT treatment would result in a worse survival. Failure to reject the null hypothesis was taken as evidence supportive of the non-IT treatment; rejection of the null hypothesis as evidence supportive of the IT treatment. To avoid the risk of accepting the non-intensive treatment too easily, we employed a significance level of 0.20 rather than the usual 0.05. Assuming a median survival of 12 weeks for the IT group, a total of 50 patients would be needed to ensure that the probability of accepting the non-intensive treatment is 5% when it results in a median survival of 6 weeks. However, because of decreasing accrual, the trial was prematurely closed after 35 patients. Therefore, in accordance with current approaches to non-inferiority trials, the 95% lower confidence bound of the difference in median survival between the 2 arms was chosen as the primary evaluation parameter. If a decrease by at least 6 weeks in median survival in the non-IT arm were to fall within this Confidence Interval (CI), the trial would be considered inconclusive with regard to the superiority of IT treatment. In addition, the more traditional two-sided 95% CI and *P*-value for the standard null hypothesis of no difference was calculated.

Median survival (differences), their standard errors (SEs) and CIs, as well as associated *P*-values were estimated using the Weibull model with equal shape parameters in both groups, which produced a satisfactory fit to the data. The accuracy of the calculations was checked by parametric bootstrapping (with variance stabilised t-interval), using 999 Monte Carlo samples of sizes 17 and 18 from the fitted Weibull curves [15]. The Weibull model was also used to evaluate the significance of the PI and its components, and of the Karnofsky performance status.

Survival curves were calculated according to Kaplan and Meier [16], with SEs from Peto [17].

Between-treatment differences in neurological response and toxicity were calculated with cross-tabulation, χ^2 tests and the Cochran–Mantel–Haenszel trend test [18], where applicable. No subgroup or interim analyses were planned or carried out. All analyses were based on intention-to-treat.

3. Results

3.1. Patient characteristics (Table 1)

Between May 1991 and July 1998, 35 patients were entered into the trial, 22 patients during the first 3 years, and 13 patients during the subsequent 4 years. It appeared difficult to obtain the patient's consent after information about randomisation between standard intensive treatment including insertion of an Ommaya reservoir with its possible complications or non-IT treatment. This became even more problematic over the years when clinical practice and other studies confirmed our previous finding that non-IT treatment might be as effective as intensive IT treatment in LM from breast cancer [8,13]. The study was closed prematurely because of this dwindling accrual. Seventeen patients were randomised to IT treatment and 18 to non-IT treatment (Fig. 1). Of the 35 patients, 34 had tumour-positive CSF cytology. One patient had negative cytology, but other CSF abnormalities and characteristic MRI findings. Imbalances between the treatment arms were age and cognitive functioning, but can still be explained by chance and do not indicate randomisation errors. At randomisation, cognitive impairment was present in 8 of the 17 IT patients, and in 3 of the 18 non-IT patients: mild changes in mental status with some apathy, disorientation and memory loss were seen in 7 IT patients, and in 3 non-IT patients, whereas one IT patient was seriously confused (Table 1). All 17 IT patients started with IT MTX. The mean number of cycles of MTX administered was 8 (range 1–21). MTX was replaced

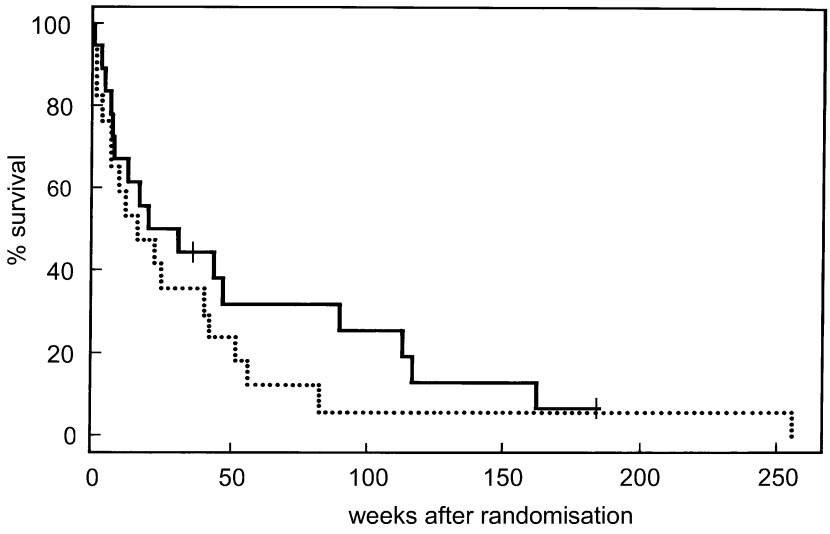

Fig. 1. Survival curves for the intraventricular treatment (IT) and non-IT group. Solid line: non-IT treatment; broken line: IT treatment.

Table 1
Patients' characteristics at randomisation

	Group 1, Intraventricular chemotherapy	Group 2, No Intraventricular treatment
Number of patients	17	18
Mean age (years; ±SD)	49.6 ± 8.8	57.9 ± 9.9
<55	12	6
⩾55	5	12
Karnofsky ± SD	64 ± 16	71 ± 19
Lung metastases	3 (18%)	5 (28%)
Previous brain metastases	2 (12%)	1 (6%)
Cranial nerve involvement	5 (29%)	8 (44%)
Cognitive impairment moderate	7 (41%)	3 (17%)
Serious	1 (6%)	0
Mean CSF protein ± SD	1.4 ± 1.4	1.7 ± 1.5
⩽0.5 g/l	3 (18%)	3 (17%)
>0.5 g/l	14 (82%)	15 (83%)
Mean CSF glucose ± SD	2.2 ± 1.2	2.8 ± 1.1
⩽2.5 mmol/l	9 (53%)	8 (44%)
>2.5 mmol/l	7 (41%)	10 (56%)
Unknown	1 (6%)	
Mean CSF cell count/mm^3 ± SD	35 ± 34	20 ± 33
Prognostic index ± SD	2.2 ± 1.6	2.7 ± 1.3

SD, standard deviation.

by intraventricular Ara-C in 3 patients (mean number of cycles of Ara-C = 10, range 4–14) because of a lack of response to MTX, MTX meningitis, and MTX leucoencephalopathy. Table 2 shows treatment given within 4 weeks after randomisation, i.e. the period that usually determines further outcome of LM [8,13]. Systemic chemotherapy included standard regimens of cyclophosphamide, doxorubicin, 5-fluorouracil, epidoxorubicin and methotrexate: (CAF, FEC and CMF). Hormonal treatment included tamoxifen, orimeten, megestrol and fluoxymesterone. Overall, systemic treatment and involved field RT did not differ essentially between the 2 treatment groups. High-dose systemic therapy with known cytotoxic penetration in the CSF was given in one non-IT patient 2 years after standard chemotherapy for LM.

Table 2
Applied therapy within 4 weeks after randomisation

	Group 1 (IT)	Group 2 (non-IT)
Intraventricular chemotherapy	17 (100%)	–
Systemic chemotherapy	7 (41%)	9 (50%)
Hormonal therapy	7 (41%)	6 (33%)
Systemic chemotherapy and hormonal therapy	–	1 (6%)
No systemic therapy	3 (18%)	2 (11%)
Involved field radiotherapy	6 (35%)	9 (50%)

IT, intraventricular treatment.

3.2. Survival (Fig. 1)

All but 2 patients died during follow-up (Fig. 1). One patient (in good neurological condition) was lost to follow-up after 36 weeks due to emigration, and one patient was still alive and well at the end of follow-up, 184 weeks after randomisation. Both of these patients were randomised to the non-IT arm, and were assumed to be uninformatively censored. Survival of the patient without cytologically-proven LM was 4 weeks. At one year, estimated survival was 18% (standard error (SE) 9%) for the IT-arm and 32% (SE 12%) for the non-IT-arm (logrank test: $P = 0.32$).

Median survival was 18.3 (SE 6.7) weeks in the IT-arm and 30.3 (SE 10.9) weeks in the non-IT arm; difference 12.9 weeks in favour of the non-IT arm by the bootstrap technique with 95% CI from −5.5 to 34.3 weeks.

We could not confirm the prognostic relevance of PI on survival in this small sample size. No significant relationship was found between survival and the individual factors of the prognostic index, or the Karnofsky performance scale. Causes of death are listed in Table 3.

3.3. Response

Seven of the 17 IT patients (41%) showed neurological improvement and 3 patients (18%) stabilisation (Table 4). Median time to neurological progression of responding or stable patients was 43 weeks (interquartile range 25–63 weeks) and of the entire group 23 weeks. At one year, 22% were free of neurological progression. Seven IT patients progressed immediately; one patient died within 1 week due to treatment complications. Eventually, 13 of the 17 patients showed neurological progression (76%). Six IT patients attained a cytological response in CSF; in 5 of them within 2 weeks of IT. Median survival of these 6 patients was 52 weeks. Two of them had a cytological relapse, with survival from relapse of 34 and 61 weeks. Of the 8 patients with cognitive impairment at baseline, the patient with serious confusion died within 1 week due to treatment complications. During treatment, moderate cognitive impairment improved in 3 patients, and remained unchanged in 4 patients.

Seven of the 18 non-IT patients (39%) responded and 5 showed stabilisation (28%). Median time to neurological progression of responding or stable patients was 64 weeks (interquartile range 16–∞ weeks), and of the entire group 24 weeks. At one year, 39% of the non-IT patients were free of neurological progression. Six patients progressed immediately; one of them died within one week due to septicaemia. Eventually, 10 of the 18 patients showed neurological progression (56%). Of the 3 patients with moderate cognitive impairment at baseline, one patient improved, one remained unchanged, and the other deteriorated further during treatment.

3.4. Toxicity

One heavily pre-treated patient who received FEC chemotherapy for LM developed permanent bone marrow suppression. A number of clinical features (e.g., headache, vomiting, gait disturbances and mental changes) may signify treatment-related toxicity, but can also be caused by LM.

Specific treatment-related neurological complications were seen almost exclusively in the IT group (Table 5). Early complications related to the insertion of the Ommaya reservoir, the intraventricular injection of MTX and CNS infections were usually transient. One patient became comatose and died within 24 h after placement of the reservoir and the subsequent intraventricular injection of 10 mg MTX. Brain CT and CSF examination including MTX concentrations were unremarkable. Post-mortem investigation was not performed.

Complications related to the Ommaya system included reservoir revision because of dysfunction,

Table 3
Causes of death

	Group 1 (IT)	Group 2 (non-IT)
Neurological disease	7/17 (41%)	7/16 (44%)
Systemic disease	4/17 (24%)	5/16 (31%)
Progressive neurological and systemic disease	4/17 (24%)	2/16 (13%)
Neurotoxicity	1/17 (6%)	1/16 (6%)
Intercurrent disease	1/17 (6%)	1/16 (6%)

Table 4
Neurological response to treatment

	IT (n = 17)	Non-IT (n = 18)
Improvement	7 (41%)	7 (39%)
Stabilisation	3 (18%)	5 (28%)
Median time to progression of responding patients (25–75% range)	43 weeks (25–63 weeks)	64 weeks (16–∞ weeks)
No response	7 (41%)	6 (33%)
Overall neurological progression	13 (76%)	10 (56%)
Overall median time to neurological progression	23 weeks	24 weeks
Free of neurological progression at one year	22%	39%

Table 5
Toxicity and complications of treatment

	Group 1 (IT)	Group 2 (non-IT)
Treated for vomiting	6 (35%)	6 (33%)
Intractable vomiting	1 (6%)	1 (6%)
Permanent myelosuppression (grade 4)	–	1 (6%)
Headache		
Mild	3 (18%)	2 (11%)
Moderate	7 (41%)	4 (22%)
Serious	2 (12%)	3 (17%)
Intractable	1 (6%)	1 (6%)
Gait disturbances		
Moderate	3 (18%)	9 (50%)
Serious/bedridden	11 (65%)	5 (28%)
Lethargy		
Moderate	7 (41%)	6 (33%)
Serious	2 (12%)	1 (6%)
Cognitive impairment		
Moderate	9 (53%)	4 (22%)
Serious	3 (18%)	2 (11%)
MTX meningitis	2 (12%)	–
Infectious meningitis	2 (12%)	–
Ommaya reservoir revision	3 (18%)	–
Intracerebral haemorrhage	1 (6%)	–
Subdural haematoma	1 (6%)	–
Acute fatal encephalopathy	1 (6%)	–
Subacute transient encephalopathy	1 (6%)	–
Delayed leucoencephalopathy	3 (18%)	1 (6%)

self-limiting intracerebral haemorrhage and bilateral subdural haematomas. Infectious meningitis developed in 2 patients, necessitating removal of the drain in both. MTX meningitis was observed in 2 patients. Transient subacute encephalopathy occurred in one patient who later developed delayed leucoencephalopathy. Delayed leucoencephalopathy occurred in 3 IT patients. These patients had received cumulative doses of 150–170 mg MTX without WBRT. Leucoencephalopathy was diagnosed at 5 months, 11 months, and 30 months from the start of IT treatment. In one patient, cognitive function deteriorated further, while in 2 patients it remained moderately impaired until death. Survival times from the diagnosis of leucoencephalopathy were 1 month, 7 months, and 29 months. Overall, 2 IT patients received WBRT, both 1 month before death. Leucoencephalopathy developed in one non-IT patient after remission of LM for 2 years following a total of 10 cycles of CMF, when she was treated for leptomeningeal relapse with WBRT followed by 3 courses of high-dose intravenous (i.v.) MTX (1 gm/m^2). Six months after WBRT she developed gait disturbances and became apathic that gradually increased until her death 4 months later. Another 4 non-IT patients received WBRT, 1–43 months before death without causing side-effects. Overall, 8 of the 17 IT patients (47%) suffered specific treatment-related neurological complications versus one of the 18 non-IT patients (6%) ($P = 0.0072$).

4. Discussion

Patients treated with IT chemotherapy for LM from breast cancer may have a better outcome when they also receive systemic chemotherapy [7,8,13]. It is possible that LM tumour deposits can be reached and treated by cytostatic drugs through their own permeable tumour blood vessels [19,20]. Moreover, non-randomised studies show that the outcome after standard systemic chemotherapy and involved field RT is similar to that following treatment including IT chemotherapy, but without the neurotoxicity associated with IT treatment [8,9]. Patients with LM from breast cancer may even show a neurological and cytological response to systemic hormonal therapy [21]. The present randomised study confirms these findings. In the current study, treatment differed only in inclusion or exclusion of IT chemotherapy. Appropriate systemic therapy and involved field RT were essentially the same in both treatment arms. Unfortunately, the study was closed well before the projected accrual of 50 patients. However, despite the small number of patients, the 95% CI for differences in median survival (−5.5 to 34.3 weeks) indicates that it is highly unlikely that omission of IT treatment will result in a decrease in median survival of 6 weeks or more, which was the predefined, clinically relevant difference. Interim analysis of patients not randomised for non-medical reasons, showing a median survival of 12 weeks for IT-treated patients and of 36 weeks for non-IT-treated patients [22] further corroborates the findings of this randomised study. This raises the question as to whether intraventricular chemotherapy should be given routinely as standard treatment for LM. Lack of improvement of neurological response provides another argument against the use of standard IT chemotherapy. The median survival of 18.3 weeks for the IT-treated patients, and, particularly, the 30.3 weeks for non-IT treated patients, compares favourably with the median survival of 8–15 weeks observed in other prospective studies of IT treatment for LM from breast cancer [5,6,11,23]. Some selection of patients may have occurred in our study because life-expectancy based on systemic tumour had to be at least 3 months. Systemic therapy given to most IT-treated patients probably also contributed to the longer survival observed.

The long-term survival in the present study also equals or exceeds the 6–19% one-year survival rate reported in the literature [8,11,24,25]. Especially the one-year survival of 32% observed in the non-IT patient group challenges the assertion that survival from LM will only be 4–6 weeks, unless it is intensively treated [1–3].

A cytological as well as neurological response was noted in 35% of IT patients, again this compares favourably with response rates of 0–36% reported in other prospective studies [6,10,11]. It also indicates that failure to observe differences in outcome between the IT and non-IT groups cannot be ascribed to poor treatment results in our IT-treated patients. Lumbar CSF was not re-examined routinely, because survival and neurological outcome were the main objectives in our study. The importance of a cytological response in patients with LM from solid tumours is questionable. It was reported that clinical response and survival in patients treated for LM were not related to a cytological response [6]. Previously, we found that outcome depended more on the neurological response than on CSF cytology [8]. In addition, in the present study, we observed long patient survival in spite of tumour-positive CSF cytology.

Several years after the start of our study, it was reported that lack of efficacy of IT treatment might be related to CSF flow obstruction [26,27]. We did not verify CSF flow in our patients, but we consider it unlikely that possible flow obstruction had a significant adverse effect on the results. In a randomised trial of IT chemotherapy [10], after exclusion of patients with flow obstruction, a response was reported in 2 of 11 breast cancer patients treated with IT depot Ara-C and in none of 11 patients treated with IT MTX, as compared with a response in 6 of 17 patients treated with IT MTX in the present study. Notably, systemic therapy circumvents the possible problem of CSF flow obstruction.

Neurological complications of IT treatment are a major issue in the treatment of LM. The incidence and type of complications observed in the current study are similar to previous reports: In a randomised trial comparing IT MTX with IT MTX/Ara-C [5] 1 patient died from post-insertion complications, in 5 of the remaining 17 patients (29%) major complications occurred related to the Ommaya reservoir (including one fatal intracranial hemorrhage), and 4 patients (24%) developed meningitis. Another randomised trial [6] reported severe complications related to IT MTX in 36% of the patients, these were life-threatening in 18%, and fatal in 4%. Other studies reported serious complications related to the Ommaya reservoir in 30% [7], and in 22% [12] of the treated patients. In a report of long-term survivors of intraventricular chemotherapy [13] 10% of the patients had been re-operated upon for reservoir revision, and 59% had developed late leucoencephalopathy, which is similar to our experience [8]. Thus, in approximately one-third of intraventricularly treated patients complications occur in the early phase of treatment that are usually manageable or self-limiting, but often require extra hospitalisation and sometimes lead to early death. Besides, it cannot be excluded that delay of adequate anticancer treatment due to early complications of IT treatment, has contributed to the slight, though non-significant difference in outcome between IT- and non-IT treated patients in the present study. In one-third or half of the few long survivors, late leucoencephalopathy develops that will often seriously affect quality of life. This study once more demonstrates that leucoencephalopathy can develop after IT MTX without WBRT [28]. We cannot exclude that CSF flow disturbances contributed to the occurrence of leucoencephalopathy. However, apart from leucoencephalopathy, the rate of other treatment-induced complications is substantially higher in IT-treated patients.

In conclusion, standard systemic treatment with involved field RT in LM from breast cancer is both feasible and ethical. IT chemotherapy can safely be withheld as it does not result in improved outcomes and is associated with increased treatment-related morbidity.

Conflict of interest statement

None declared.

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