Meningeal Carcinomatosis in Patients with Breast Carcinoma

Clinical Features, Prognostic Factors, and Results of a High-Dose Intrathecal Methotrexate Regimen

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This work was presented in part at the 19th ESMO Congress, Lisbon, Portugal, November 18–22, 1994 and at the 17th San Antonio Breast Cancer Symposium, San Antonio, Texas, December 8–10, 1994.

The authors thank Mrs. Lorna Saint Ange and Martine Coutant for editorial and technical assistance.

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Received May 1, 1995; revision received December 4, 1995; accepted December 4, 1995.

BACKGROUND. This retrospective study evaluates the results of a regimen of high-dose intrathecal methotrexate and the prognostic factors for response in patients with meningeal metastases from breast carcinoma.

METHODS. From 1979 to 1994, 68 breast carcinoma patients were diagnosed with meningeal carcinomatosis at a mean age of 52 years. All but two had previous metastatic involvement. The proportion of lobular and ductal carcinomas was balanced. Malignant cells were present in cerebrospinal fluid (CSF) samples from 61 patients, whereas the 7 remaining patients had increased CSF protein associated with computerized tomographic scan evidence of meningeal metastases. From 1989, 41 of the patients received a regimen of high-dose intrathecal methotrexate with systemic folinic acid rescue (HD-MTX+FA): intrathecal MTX, 15 mg daily × 5 days, repeated every 2 weeks, and intrathecal hydrocortisone acetate, 125 mg on Day 1, and folinic acid, 10 mg intramuscularly 12 hours after each MTX injection. Systemic treatment and radiation therapy were usually associated. Patients treated before 1988 received intrathecal MTX in conventional doses (15 mg once a week).

RESULTS. Clinical objective response, defined as a neurological improvement for at least one month, was achieved in 17 patients (41%) and stabilization in 14 (34%) treated with the HD-MTX+FA regimen. The response rate was significantly higher compared with that of the group treated with conventional doses ($P = 0.03$). Median survival was 14 weeks for patients treated with the HD-MTX+FA regimen, compared with 7 weeks for patients who received conventional doses of MTX ($P = 0.01$). Grade 3 or 4 neutropenia was the main toxicity that occurred in 16 patients (39%) treated with the HD-MTX+FA regimen, and in 7 patients (33%) treated with conventional doses of MTX. In a univariate analysis, three parameters were singled out as having a favorable prognostic value for response to therapy: controlled systemic disease at diagnosis ($P < 0.05$), low initial CSF protein level ($P < 0.05$), and concomitant systemic chemotherapy during intrathecal therapy ($P < 0.02$). Multivariate analysis was not performed because the sample size was too small.

CONCLUSIONS. Although this study was retrospective, the intrathecal HD-MTX+FA regimen appears to be a more efficient strategy than conventional doses of MTX to induce neurologic improvement and perhaps better survival. It should be recommended in combination with systemic chemotherapy for selected patients with meningeal carcinomatosis from breast carcinoma who are likely to benefit from intensive therapy, i.e., patients with a CSF protein level less than 5 g/L and in whom systemic disease has been controlled. ***Cancer* 1996; 77:1315–23.** © *1996 American Cancer Society.*

KEYWORDS: meningeal carcinomatosis, leptomeningeal metastases, intrathecal methotrexate, prognostic factor, breast carcinoma, lobular carcinoma, chemotherapy.

Breast carcinoma is probably the leading solid tumor responsible for meningeal carcinomatosis (MC).[1] The prognosis for patients with MC is poor and intrathecal treatment provides only a short prolongation of survival.

The aim of this study was: (1) to evaluate clinical and biologic data from a large series of patients with MC from breast carcinoma; (2) to determine prognostic factors for response to therapy; and (3) to compare retrospectively, both in terms of response and survival, the results of two treatment protocols used in the Institut Curie between 1979 and 1994: low-dose (conventional) intrathecal methotrexate (1979–1988) and high-dose intrathecal methotrexate associated with systemic folinic acid rescue (1989–1994).

PATIENTS AND METHODS

Patient Characteristics

The records of 68 patients with breast carcinoma and meningeal carcinomatosis (MC) admitted to the Institut Curie, Paris, between 1979 and 1994 were reviewed. They ranged in age from 27 to 77 years (mean: 52 years). The interval between primary tumor and diagnosis of MC ranged from 10 to 331 months (mean: 66 months). Tumor-related data are shown in Table 1. Slides were reviewed by one of the authors (A.V.S). The proportion of lobular carcinoma and ductal carcinoma was balanced, whereas most patients had negative estrogen receptors (ER) as well as negative progesterone receptors (PR) and nuclear Grade 2. The bone was the most frequent site of metastasis. Only two patients had no detectable site of metastasis other than the meninges. Most of the patients (92%) had received systemic chemotherapy for metastatic disease and all of them had received chemotherapy as either a neoadjuvant or adjuvant strategy. Neurologic signs or symptoms were present in 67 of 68 patients, and were multipled in 61 of 68 patients. The distribution of signs and symptoms is detailed in Table 2. Since 1983, most of the patients were investigated with a computerized tomographic (CT) brain scan, and, since 1989, with contrast-enhanced brain magnetic resonance imaging (MRI).

CSF Findings

Malignant cells were observed in CSF obtained by lumbar puncture from 61 patients (90%). The remaining seven patients had an increased CSF protein level associated with CT scan evidence of meningeal abnormalities consistent with tumor involvement. CSF cytology was positive at the initial puncture in 39 patients (59%) and, after three punctures, in 52 patients (79%) (Table 3). The initial CSF protein level was increased in 80% of the evaluated patients.

Intrathecal Treatment

Patients were treated differently according to the reference period. Between 1979 and 1988, 21 patients were given methotrexate via the intrathecal route at a dose of 15 mg once a week (low-dose methotrexate or LD-MTX) combined with 125 mg of hydrocortisone acetate. Between 1989 and 1994, 41 patients were given high-dose methotrexate (HD-MTX) intrathecally as follows: 15 mg once a day for 5 days followed by 9 days without treatment. Hydrocortisone acetate was injected intrathecally on the first day of the 2-week cycle in order to minimize arachnoiditis. Ten milligrams of folinic acid (FA) were given via the intramuscular route 12 hours after each MTX injection (Fig. 1). Treatment cycles were repeated every 2 weeks. MTX administration was continued until neurologic progression or relapse occurred, or as long as the patient's general medical condition permitted treatment.

During the same period (1989–1994), 6 patients did not receive HD-MTX+FA. One of them did not receive it because she died 3 days after diagnosis of MC. Another patient had progressive liver disease with icterus and was treated by palliative radiation therapy directed to meningeal masses and survived 1 month. The remaining four patients had localized brain or meningeal metastases that required whole brain irradiation. Thus, thiotepa was given at a dose of 10 mg twice a week instead of MTX to prevent neurologic toxicity. Their survival ranged from 5 to 17 weeks. Most of the patients were treated with repeated lumbar punctures, whereas 6 (9%) underwent placement of an Ommaya reservoir.

Other Treatments (Table 4)

Systemic chemotherapy was routinely administered in case of symptomatic systemic metastases. Two schedules, both based on continuous 5-fluorouracil (FU) infusion, were used: (1) Fucontin: (cyclophosphamide, vindesine, and 5-FU) for cases of bone marrow involvement or in highly pretreated patients; (2) Fulon: modified FAC schedule: (adriamycin, cyclophosphamide, and continuous 5-FU infusion). Patients with symptomatic meningeal masses detected by CT scan underwent either cranial, spinal, or craniospinal radiation therapy.

Oral corticosteroids were also routinely prescribed. When symptomatic brain or meningeal metastatic masses occurred during patient management, radiation therapy was delivered. In these cases, intrathecal chemotherapy was stopped one week before radiotherapy and resumed one week after.

Evaluation and Response Criteria

Response assessment included a twice-monthly neurologic examination, and a biologic examination of a CSF sample obtained before each drug injection.

A clinical response was defined as clear evidence of

TABLE 1
Pretreatment Tumor Data of 68 Patients with Meningeal Carcinomatosis from Breast Carcinoma

	Overall n = 68	LD-MTX (1979–1988) n = 21	HD MTX + FA (1989–1994) n = 41
Pathological data			
• ductal carcinoma	29 (49%)	9 (47%)	17 (49%)
• lobular carcinoma	29 (49%)	9 (47%)	18 (51%)
• others	1 (2%)	1 (5%)	0
• unknown	9	2	6
Estrogen receptor			
• positive	13 (39%)	1	10 (45%)
• negative	20 (61%)	5	12 (55%)
• unknown	35	15	19
Progesterone receptor			
• positive	11 (31%)	4	5 (20%)
• negative	25 (69%)	3	20 (80%)
• unknown	32	14	16
Nuclear grade (Scarff-Bloom-Richardson)			
• 1	7 (13%)	2 (12,5%)	5 (16%)
• 2	27 (51%)	10 (62,5%)	12 (37%)
• 3	19 (36%)	4 (25%)	15 (47%)
• unknown	15	5	9
Activity of systemic disease			
• progressive disease	30 (44%)	7 (33%)	17 (41%)
• responsive and stable disease	34 (53%)	13 (62%)	23 (56%)
• no evidence of systemic disease	2 (3%)	1 (5%)	1 (2%)
Systemic metastases			
• bone	47 (69%)	13 (62%)	28 (68%)
• liver	20 (29%)	4 (19%)	14 (34%)
• lung	17 (25%)	7 (33%)	9 (22%)
• brain	16 (23%)	2 (10%)	13 (32%)
• skin	10 (15%)	3 (14%)	6 (15%)
• epidural	5 (7%)	3 (14%)	2 (5%)
• other (including lymph nodes)	15 (22%)	3 (14%)	11 (27%)

resolution of either some or all neurologic signs or symptoms for a duration of at least one month, in the absence of a concomitant decline in neurologic status. Clinical stabilization was defined as the absence of any deterioration or improvement of neurologic signs or symptoms, and progression was defined as a worsening of neurologic status. Relapse was defined as a deterioration in neurologic symptoms occurring after an initial clinical response.

Two consecutive negative CSF samples were considered a criterion for a cytologic response. Toxicity was based on WHO criteria.[3] Survival was measured from the date of the first intrathecal drug injection to the date of death or the last date the patient was known to be alive.

Statistical Analysis

The χ^2 test was used to compare qualitative data from the treatment groups and to analyze response data. The Student's t test was used to compare quantitative data. The Kaplan–Meier method was used to calculate survival curves. Both the log rank test[4] and the generalized Wilcoxon test[5] were used to test the differences between curves.

RESULTS

Response

In the HD-MTX+FA group, 17 patients attained a clinical response (41%), 14 attained stabilization (34%), and 10 experienced progression (25%). In the LD-MTX group, only 3 patients experienced neurologic improvement (14%), 10 had stable disease (48%), and 8 showed evidence of neurologic deterioration (38%). The response rate on HD-MTX-FA was significantly higher than on LD-MTX (41% vs. 14%; $P = 0.03$).

The mean time to clinical response was 30 days from the start of intrathecal treatment (range: 2–68 days), and the mean duration of clinical improvement was 128 days.

Fifteen patients in the HD-MTX+FA group switched from a positive to a negative CSF cytology (cytologic response): 10 experienced clinical improvement, 4 clinical stabilization, and 1 progression.

TABLE 2
Clinical Data of 68 Patients with Meningeal Carcinomatosis from Breast Carcinoma

	Overall (%) n = 68	LD-MTX (%) n = 21	HD MTX + FA n = 41 (%)
Mean age	52	51	51
Performance status			
1	18 (27%)	7 (33%)	11 (27%)
2	28 (42%)	8 (32%)	18 (44%)
3	21 (31%)	6 (29%)	12 (29%)
unknown	1	0	0
Prior chemotherapy for metastatic disease	62 (92%)	19 (90%)	38 (93%)
Neurological signs and symptoms			
• Weakness	32 (48%)		
• Headache	31 (46%)		
• Paresthesia	30 (45%)		
• Cerebellar signs (ataxia)	15 (22%)		
• Nausea vomiting	15 (22%)		
• Back pain or radicular pain	14 (21%)		
• Stiff neck	13 (19%)		
• Cranial nerve palsies	12 (18%)		
• Confusion	10 (15%)		
• Somnolence	9 (13%)		
• Change in vision	6 (9%)		
• Dysarthria	4 (6%)		
• Seizure	3 (4%)		

Factors Predictive of Clinical Response

Pretreatment patient characteristics and treatment-related parameters were tested to predict clinical response. The histopathologic type, nuclear grade, prior systemic chemotherapy, age, performance status, time from the primary, type of neurologic signs or symptoms, radiation therapy, and hormonotherapy were not predictors of response. Conversely, 3 parameters were predictive of clinical response: (1) the status of systemic disease prior to diagnosis of MC (18% of the patients with progressive systemic disease achieved a clinical response vs. 42% of the patients with stable or responding disease; $P < 0.05$); (2) the initial CSF protein level (mean 1.6 g/L for responders vs. 4.7 g for nonresponders; $P < 0.05$); (3) concomitant systemic chemotherapy (42% of the patients with concomitant chemotherapy achieved a clinical response vs. 13% of the patients without concomitant chemotherapy; $P < 0.02$). Moreover, there were no responders in the group of 9 patients with an initial CSF protein level greater than 5 g/L (5 g/L = 500 mg %), versus 49% in the group of patients with an initial CSF protein level less than 5 g/L ($P < 0.03$).

Survival

Median survival for the entire group of 68 patients was 67 days. Ten patients survived for more than a year. The longest duration of survival was 868 days with a mean of 183 days.

Patients from the LD-MTX group had a median survival of 49 days (confidence interval (CI): 32–67) compared with a median of 98 days (CI: 53–179) for patients from the HD-MTX+FA group (Fig. 2). This difference is statistically significant with the generalized Wilcoxon test ($P = 0.01$), but not with the Mantel–Cox method ($P = 0.16$).

Cause of Death

At time of the analysis, 60 patients had died. The main causes of death were distributed as follows: MC: 63%; systemic disease: 45%; others (in particular, infection unrelated to therapy): 22%. Death was frequently due to multiple causes. Treatment-related neutropenia was implicated in 6% of the cases.

Toxicity (Table 5)

The most frequent toxicity was neutropenia, which occurred in more than one-third of the patients. This is not surprising for highly pretreated patients. Neutropenia was frequently complicated by infection and was one of the main causes of death in 7 of the patients (3 in the LD-MTX group and 4 in the HD-MTX+FA group). Grade 3 or 4 mucositis was rare.

TABLE 3
CSF Data of 68 Patients with Meningeal Carcinomatosis from Breast Carcinoma

	Overall (%) n = 68	LD-MTX n = 21	HD MTX + FA n = 41
Initial CSF protein			
> 0.5 g/l	41 (80%)	12	25
< 0.5 g/l	10 (20%)	1	7
unknown	17	8	9
Initial CSF glucose			
< 2.5 mmol/l	6	0	6
> 2.5 mmol/l	19	6	10
unknown	43	15	25
OMMAYA reservoir	6	3	2
No. of punctures before positive cytology			
1	39 (59%)		
2	8 (12%)		
3	5 (8%)		
>3	9 (13%)		
negative cytology	7 (10%)		
Number of intrathecal injections			
mean (range)		7,7 (1-36)	19 (4-76)

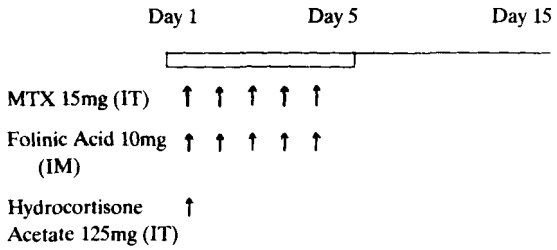

FIGURE 1. HD-MTX+FA: treatment protocol.

Our patients exhibited periventricular hypodensity on systematic CT scan of the brain but cognitive function was not impaired. In the LD-MTX group, a case of purulent meningitis due to a *Staphylococcus aureus* had a favorable outcome after antibiotherapy.

Aseptic meningitis, which was always asymptomatic, was frequent and characterized by pleocytosis of granulocytes in the CSF, with negative CSF cultures.

DISCUSSION

Although breast cancer is probably the leading solid tumor to cause MC,[1,6] few reports have focused exclusively on this association.[7-12] To our knowledge, this is the largest series of MC associated with breast carcinoma. The incidence of MC in breast carcinoma patients accounts for 1% to 5% in most clinical studies.[9,11-15] In an autopsy study, Tsukada et al.[16] reported an incidence of about 5.6%.

TABLE 4
Nonintrathecal Associated Treatments of 68 Patients with Meningeal Carcinomatosis from Breast Carcinoma

	Overall (%) n = 68	LD-MTX (%) n = 21	HD MTX + FA n = 41 (%)
Prior chemotherapy	62 (92%)	19 (90%)	38 (93%)
CNS radiation therapy	18 (26%)	4 (19%)	10 (24%)
Systemic chemotherapy	42 (62%)	13 (62%)	28 (68%)
• FUCONTIN protocol	23	6	16
• FULON protocol (including doxorubicin)	19	7	12
Hormonotherapy	8 (12%)	5 (24%)	3 (7%)
No treatment (except intrathecal CT)	19 (28%)	6 (29%)	11 (27%)

MC is a late event in the natural history of breast cancer: mean time to diagnosis is 66 months. Ninety-seven percent of our patients had other metastatic sites before MC, and all of them had already received chemotherapy. Patients without metastatic disease, other than MC, are, however, regularly reported in the literature, with an incidence ranging from 2% to 30%.[7-9,11,15,17] As previously reported, the bone was the main site of metastasis,[9,11] thus underlining possible direct extensions from vertebral lesions to leptomeninges.[18] Lobular carcinoma seems to be more frequently associated with MC than expected, as previously reported in an autopsy study[19] and recently reported in a clinical study.[12] Most of the patients had negative ER or PR (respectively, 61% and 69%), which seems to be a higher proportion than that found in the general population of women with metastatic breast cancer.[20] The nuclear grade was 2 or 3 in 87% of the patients.

At diagnosis of MC, patients had a wide variety of neurologic symptoms or signs. This emphasizes the need for a diagnostic lumbar puncture in all of the patients with obscure neurologic manifestations to exclude meningeal involvement. However, weakness, headache, and paresthesia were the main symptoms in our series, as previously reported by Grossman et al.[21] The first lumbar puncture was positive in only about 60% of the patients, and 79% of the cases of MC were diagnosed after three successive punctures. Few other cases were diagnosed after three punctures. We decided to treat certain patients in the absence of documented positive cytology, when clinical data, an elevated CSF protein level, and abnormalities on CT scan were consistent with the diagnosis of MC, as recommended by others.[6] CSF protein was very frequently elevated, as previously reported,[11,15] and seems to be one of the most sensitive characteristics of MC.

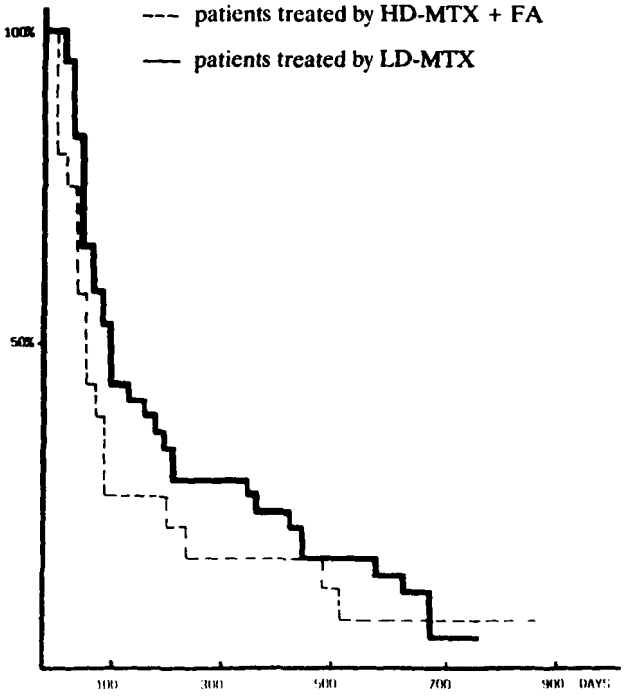

FIGURE 2. Survival curves.

Most of our patients were treated via lumbar puncture. The rationale was based on the following: (1) Boogerd et al. have shown that the median survival in patients treated intraventricularly or nonintraventricularly;[11] (2) ventricular CSF cytologic samples are frequently false-negative compared with lumbar CSF samples;[11] (3) major physical complications related to the Ommaya reservoir, including intracranial hemorrhage,[14,22,23] purulent meningitis,[8,11,14,22-24] and death[11,14,22,23,25] are not rare; and (4) the median survival of unselected patients with MC and breast carcinoma is too short to justify systematic Ommaya reservoir implantation. We suggest that patients with favorable pretreatment data, i.e., controlled systemic disease and a normal CSF protein level, should be good candidates for Ommaya reservoir implantation.

Only three chemotherapeutic drugs are routinely used for intrathecal administration in patients with MC from breast carcinoma: methotrexate, thiotepa, and cytosine arabinoside.[26-28] In a recent randomized study, Grossman et al.[21] found no difference in terms of efficacy between methotrexate and thiotepa. Moreover, multiagent intrathecal administration does not seem to improve response compared with single-agent therapy.[14,29,30] With respect to the poor outcome of these patients, the discussion on the interest of vigorous treatment is still open since most authors recommend its use in MC from breast carcinoma.[6,7,10,15] Sorensen et al. and, more recently, Grant et al., have criticized the real benefit derived from aggressive therapy compared with symptomatic management.[17,31] However, it is difficult to reach firm conclusions about the ineffectiveness of aggressive treatment based on their studies because of the wide diversity of therapeutic modalities used. As discussed later, our results are consistent with a benefit for both intrathecal and systemic intensive therapy, although this study was not randomized.

TABLE 5
Toxicity

	LD-MTX n = 21		HD-MTX + FA n = 41	
Mucositis				
-Grade 3	0		2	
-Grade 4	0		1	
Neutropenia				
-Grade 3	3	33%	4	33%
-Grade 4	4		12	
Neurologic	0		1	
Purulent meningitis	1		0	
Pain related to drug injection	0		0	

Our regimen of intrathecal HD-MTX with folinic acid rescue was based on the following rationale. First, Bleyer et al. showed that a "concentration × time" schedule of methotrexate is less neurotoxic and equally effective as single injections in the treatment of CNS localization of leukemia.[32] Second, CSF folinic acid concentrations remain low during systemic rescue and both avoid systemic toxicity and preserve the cytocidal activity of intrathecal methotrexate.[33] Third, Boogerd et al. underlined the lack of a relationship between the intensity of methotrexate and the duration of the improvement after the first six weeks.[11] This argues in favor of early dose escalation to improve the clinical results of intra-CSF methotrexate injections. In a nonrandomized study, Ongerboer de Visser et al. found that patients initially treated with daily MTX, injected according to CSF-MTX levels, had both a better response rate and survival than patients treated with whole brain irradiation associated with low-dose MTX or untreated patients.[8] As it is difficult to activate a randomized study in patients with MC from breast carcinoma, we chose to compare, retrospectively, the results of the HD-MTX+FA regimen to our historical series of patients treated with LD-MTX. Our results show that three-fourths of the patients treated with the HD-MTX+FA schedule experienced clinical improvement or stabilization. Moreover, the response rate of 41% achieved by this group of patients is significantly higher than that of patients treated with LD-MTX ($P = 0.03$). This regimen of intrathecal HD-MTX with leucovorin rescue, associated with low dose systemic chemotherapy, compares favorably with LD-MTX and other regimens reported in the literature[6,14,17,21,30] in its ability to induce neurologic improve-

ment, although clinical response criteria are heterogeneous.

However, resistance to treatment—either initial or acquired—is very frequent and most responders relapse when they do not die from systemic disease. Causes of failure include initial or acquired drug-resistance, particularly in our series of patients pretreated with multiple agents, inadequate distribution throughout the CSF due to abnormalities in CSF flow,[34] and the failure of intrathecal chemotherapy to penetrate bulky meningeal lesions in depth.[35] In our series, MC was the cause of death in 63% of the cases, but was frequently associated concomitantly with systemic progression or sepsis.

Since 1986, systemic chemotherapy is often combined with intrathecal chemotherapy in the treatment protocol for MC from breast carcinoma,[10,11,17,25,29,30] whereas it was rare before. The use of systemic chemotherapy is logical because many patients have progressive systemic disease. Breast carcinoma is a chemosensitive neoplasm and the blood-brain barrier has been reported to be disrupted in MC.[36]

However, in an experimental model of MC, Siegal et al. showed that the CSF adriamycin level is low at (i.v.) therapeutic doses whereas lethal systemic doses are required for significant drug penetration.[37] Our experience shows that systemic chemotherapy probably has its place in the therapeutic management of MC in breast carcinoma, although clinical results are still poor. In the univariate analysis, the addition of systemic chemotherapy to intrathecal MTX appears to be a favorable factor of clinical response ($P < 0.02$). Symptomatic improvement or longer survival for patients with MC from breast carcinoma treated with systemic chemotherapy has recently been underlined.[11,17] In our opinion 5-FU continuous infusion-based regimens should be recommended in this situation of highly pretreated patients because they yield an interesting response or stabilization rate with mild toxicity.[2]

The impact of CNS radiotherapy is controversial. Two studies reported better response rates for irradiated patients[14,25] but their results were biased by patient selection: the group of irradiated patients contained a wide variety of malignancies, more radiosensitive and more previously nonirradiated tumors, a better performance status, and patients who died early during intrathecal treatment were censored from the final analysis. In a larger and more recent study, Boogerd et al. found no influence of CNS radiotherapy on survival time. He did, however, find constant late neurologic toxicity in survivors having received irradiation for more than 4 months.[11] In our series, irradiation did not confer an advantage in terms of clinical response. Further studies are required on CNS radiotherapy to assess its value in MC.

In our series, the main toxicity was hematologic as in other reports.[24,30] This underscores the need to systematically reduce standard doses of systemic chemotherapy when combined with intrathecal chemotherapy in highly pretreated patients. Of note, there was no case of infectious meningitis in patients treated with the HD-MTX+FA regimen, although these patients received a mean of 11 MTX injections compared with only 7 injections in the LD-MTX group. Infectious meningitis, mainly due to *Staphylococcus*, is regularly reported during the treatment of MC.[8,11,14,22,24,25] A favorable outcome usually ensues after appropriate antibiotherapy but deaths have been reported.[11,22]

Disseminated necrosing leukoencephalopathy is a well known delayed toxic effect following intrathecal MTX administration.[6–8,11,25,38] Its clinical presentation is hard to differentiate from the manifestations related to MC itself.[30] The clinical diagnosis of leukoencephalopathy is difficult and has probably been under estimated in our series. One of our patients treated with both HD-MTX+FA and radiotherapy had typical periventricular hypodensity on brain CT scan without neurologic symptoms. The combination of intrathecal MTX and whole brain radiotherapy dramatically increases the occurrence of leukoencephalopathy[38,39] and a transient febrile reaction following MTX administration seems to signal its imminence.[39] The low rate of this serious complication in our series may be explained by the fact that about three-fourths of the patients did not receive radiotherapy, which, when performed, was always delayed after MTX administration.

Three parameters were singled out which are favorable indicators of a clinical response: controlled systemic disease, a low CSF protein level, and treatment modalities including systemic chemotherapy. In the literature, most of the studies have reported prognostic factors for survival[7,9,11,12,14,21] and only a few have investigated prognostic indicators of neurologic improvement.[7,40] Yap et al. found that low CSF glucose and elevated CSF protein levels had an unfavorable influence on clinical response.[7] More recently, Grant et al. reported the potential role of systemic chemotherapy in the improvement of neurologic symptoms[17] whereas Boogerd et al. reported a better survival rate for patients receiving systemic chemotherapy.[11]

Although our statistical analysis did not include a multivariate study, the three simple parameters we identified ought to be used in clinical practice to select patients who would benefit from an intensive intrathecal regimen such as HD-MTX+FA.

Conversely, patients with a CSF protein level greater than 5 g/L should not be treated according to the HD-MTX+FA regimen, because their symptoms are never improved, and a less toxic regimen or palliative care would be more appropriate.

The survival of patients with MC from breast carcinoma remains short and ranges from 1.5 to 7.2 months.[6,7,9,11,12,15,20,25,30] Series reporting longer survival are biased by patient selection[6] and the real median survival is probably about 3 months.[11,12,39] Our results show a better survival for patients treated with the HD-MTX+FA regimen than those treated with LD-MTX. The difference is statistically significant ($P = 0.01$) using the generalized Wilcoxon test, which highlights early events more than the Mantel–Cox model. However, this was not a randomized study and 6 patients from the 1989–1994 period were excluded from the HD-MTX+FA study for diverse reasons.

In conclusion, the HD-MTX+FA regimen seems to improve the neurologic status of patients with MC from breast carcinoma, including potential survival. It should be used only in patients selected according to prognostic factors for response, because of its hematologic toxicity associated with systemic chemotherapy. Intensive treatment probably affords an improvement of neurologic symptoms and the quality of life, but this last point needs to be evaluated in further studies. In the meantime, effective treatment is dramatically needed to improve the outcome of patients with MC from breast carcinoma.

REFERENCES

1. Kaplan JG, Desouza TG, Farkash A, Shafran B, Pack D, Rehman F, et al. Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas and leukemia. *J Neurooncol* 1990;9:225–9.
2. Pouillart P, Palangie T, Scholl S, Belli L, Beuzeboc P, Jouve M, et al. Association de 5 fluorouracile administré en perfusion continue, de vindesine et de cyclophosphamide dans le traitement des cancers du sein métastasés. Etude de la réponse selon les sites métastatiques. *Bull Cancer* 1989;76: 191–5.
3. WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization, 1979:319. WHO Offset Publication No. 48.
4. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163–70.
5. Breslow N. A generalized Kruskal-Wallis test for comparing *K* samples subject to unequal patterns of censorship. *Biometrika* 1970;57:579–94.
6. Wasserstrom WR, Glass P, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients. *Cancer* 1982;49:759–72.
7. Yap HY, Yap BS, Rasmussen S, Levens ME, Hortobagyi GN, Blumenschein GR. Treatment for meningeal carcinomatosis in breast cancer. *Cancer* 1982;49:219–22.
8. Ongerboer de Visser BW, Somers R, Nooyen WH, Van Heerde P, Hart AAM, McVie G. Intraventricular methotrexate therapy of the leptomeningeal metastasis from breast carcinoma. *Neurology* 1983;33:1365–72.
9. Clamon G, Doebbeling B. Meningeal carcinomatosis from breast cancer: spinal cord versus brain involvement. *Breast Cancer Res Treat* 1987;9:213–7.
10. Schabet M, Kloeter I, Adam T, Heidemann E, Wiethöcter H. Diagnosis and treatment of meningeal carcinomatosis in ten patients with breast cancer. *Eur Neurol* 1986;25:403–11.
11. Boogerd W, Hart AAM, Van der Sande JJ, Engelsman E. Meningeal carcinomatosis in breast cancer. Prognostic factors and influence of treatment. *Cancer* 1991;67:1685–95.
12. Jayson GC, Howell A, Harris M, Morgenstern G, Chang J, Ryder W. Carcinomatous meningitis in patients with breast cancer. An aggressive disease variant. *Cancer* 1994;74:3135–41.
13. Gonzalez-Vitale JC, Garcia-Bunnel R. Meningeal carcinomatosis. *Cancer* 1976;37:2906–11.
14. Hitchins RN, Bell DR, Woods RL, Levi JA. A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. *J Clin Oncol* 1987;5:1655–62.
15. Yap HY, Yap BS, Tashima CK, Di Stefano A, Blumenschein GR. Meningeal carcinomatosis in breast cancer. *Cancer* 1978;42:283–6.
16. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. *Cancer* 1983;52:2349–54.
17. Grant R, Naylor B, Greeberg HS, Junck L. Clinical outcome in aggressively treated meningeal carcinomatosis. *Arch Neurol* 1994;51:457–61.
18. Kokkoris CP. Leptomeningeal carcinomatosis: how does cancer reach the piaarachnoid? *Cancer* 1983;51:154–60.
19. Harris M, Howell A, Chrissohou M, Swindell RIC, Hudson M, Sellwood RA. A comparison of the metastatic pattern of infiltrating lobular carcinoma and infiltrating duct carcinoma of the breast. *Br J Cancer* 1984;50:23–30.
20. McGuire WL. Current status of oestrogen receptors in human breast cancer. *Cancer* 1975;36:638–44.
21. Grossman SA, Finkelstein DM, Ruckdeschel JC, Trump DL, Moynihan T, Ettinger DS. Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. *J Clin Oncol* 1993;11:561–9.
22. Lishner M, Perrin RG, Feld R, Messner HA, Tuffnel PG, Path FRC, et al. Complications associated with Ommaya reservoirs in patients with cancer. *Arch Intern Med* 1990;150:173–6.
23. Obbens EAMT, Leavens ME, Beal JW, Lee Y. Ommaya reservoirs in 387 cancer patients: a 15-year experience. *Neurology* 1985;35:1274–8.
24. Trump DL, Grossman A, Thompson G, Murray K. CSF infections complicating the management of neoplastic meningitis. Clinical features and results of therapy. *Arch Intern Med* 1982;142:583–6.
25. Steward DJ, Maroun JA, Hugenholtz H, Benoit B, Girard A, Richard M, et al. Combined intraommaya methotrexate, cytosine arabinoside, hydrocortisone and thio-TEPA for meningeal involvement by malignancies. *J Neuro Oncol* 1987; 5:315–22.
26. Shapiro WR, Posner JB, Ushio Y, Chernik NL, Young DF. Treatment of meningeal neoplasms. *Cancer Treat Rep* 1977;61:733–43.
27. Gutin PH, Levi JA, Wiernik PH, Walker MD. Treatment of malignant meningeal disease with intrathecal thio-TEPA: a phase II study. *Cancer Treat Rep* 1977;61:885–7.
28. Fulton DS, Levin VA, Gutin PH, Edwards MSB, Seager ML, Stewart J, et al. Intrathecal cytosine arabinoside for the treatment of meningeal metastases from malignant brain tumors and systemic tumors. *Cancer Chemother Pharmacol* 1982;8: 285–91.

29. Nakagawa H, Murasawa A, Kubo S, Nakajima S, Nakajima Y, Izumoto S. Diagnosis and treatment of patients with meningeal carcinomatosis. *J Neuro Oncol* 1992;13:81–9.
30. Giannone L, Greco FA, Hainsworth JD. Combination intraventricular chemotherapy for meningeal neoplasia. *J Clin Oncol* 1986;4:68–73.
31. Sorensen SC, Eagan RT, Scott M. Meningeal carcinomatosis in patients with primary breast or lung cancer. *Mayo Clin Proc* 1984;59:91–4.
32. Bleyer WA, Poplack DG, Simon RG. "Concentration × time" methotrexate via a subcutaneous reservoir: a less toxic regimen for intraventricular chemotherapy of central nervous system neoplasms. *Blood* 1978;51:835–42.
33. Mehta BM, Glass JP, Shapiro WR. Serum and cerebrospinal fluid distribution of 5-methyltetrahydrofolate after intravenous calcium leucovorin and intra-Ommaya methotrexate administration in patients with meningeal carcinomatosis. *Cancer Res* 1983;43:435–8.
34. Grossman SA, Trump DL, Chen DCP, Thompson G, Camargo EE. Cerebrospinal fluid flow abnormalities in patients with neoplastic meningitis. *Am J Med* 1982;73:641–7.
35. Blasberg RG, Patlak C, Fenstermacher JD. Intrathecal chemotherapy: brain tissue profiles after ventriculo-cisternal perfusion. *Pharm Exp Ther* 1975;195:73–83.
36. Ushio Y, Shimizu K, Aragaki Y, Arita N, Hayakawa T, Mogami H. Alteration of blood-CSF barrier by tumor invasion into the meninges. *J Neurosurg* 1981;55:445–9.
37. Siegal T, Sandbank U, Gabizon A, Siegal T, Mizrachi R, Ben-David E, et al. Alteration of blood-brain-CSF barrier in experimental meningeal carcinomatosis. A morphologic and adriamycin-penetration study. *J Neuro Oncol* 1987;4:233–42.
38. Bleyer WA. Neurologic sequelae of methotrexate and ionizing radiation: a new classification. *Cancer Treat Rep* 1981;65:89–98.
39. Boogerd W, Van der Sande JJ, Moffie D. Acute fever and delayed leukoencephalopathy following low dose intraventricular methotrexate. *J Neurol Neurosurg Psychiatry* 1988;51:1277–83.
40. Sause WT, Cowley J, Eyre HJ, Rivkin SE, Pugh RP, Quagliana JM, et al. Whole brain irradiation and intrathecal methotrexate in the treatment of solid tumor leptomeningeal metastases. A Southwest Oncology Group study. *J Neuro Oncol* 1988;6:107–12.