

## Clinical symptoms and prognostic factors in breast cancer - related carcinomatous meningitis

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*Introduction.* Carcinomatous meningitis is an uncommon but serious complication of advanced breast cancer, the incidence of which has been, recently, increasing.

*Material and methods.* We have reviewed 25 cases of carcinomatous meningitis in breast cancer patients treated in our clinic. The mean age at the time of diagnosis was 45 years (range: 29-70 years). The clinical symptoms at the time of diagnosis were headache, nausea/vomiting, confusion, cerebellar signs, paresis and pain in the thoraco-lumbar region. Cancer cells in cerebrospinal fluid were detected in all the cases. Cerebrospinal fluid protein level was elevated in 72% of cases. The treatment consisted of intrathecal injection of 10 mg of methotrexate plus dexamethasone 4 mg, administered weekly.

*Results.* The response defined as clinical and laboratory improvement was achieved in 72% of patients.

*Conclusion.* Our observations suggest that the important prognostic factors in carcinomatous meningitis are: systemic chemotherapy, Karnofsky status at the time of diagnosis and the clinical response after the first 2 cycles of intrathecal infusion of methotrexate.

### Analiza objawów klinicznych i czynników prognostycznych w nowotworowym zapaleniu opon mózgowo-rdzeniowych u chorych na raka piersi

*Wprowadzenie.* W ostatnim czasie obserwuje się wyraźny wzrost ilości występowania nowotworowego zajęcia opon mózgowo-rdzeniowych wśród chorych na raka piersi. Rokowanie u pacjentek z tą lokalizacją zmian przerzutowych jest bardzo złe.

*Materiał i metody.* W naszej pracy przeanalizowaliśmy 25 przypadków pacjentek z nowotworowym zajęciem opon mózgowo-rdzeniowych. Średnia wieku wynosiła 45 lat (od 29 do 70). Objawy kliniczne, które występowały w momencie rozpoznania, to: bóle głowy, nudności i wymioty, splątanie, zespół mózdkowy, niedowład, bóle w okolicy piersiowo-lędźwiowej. W 100% przypadków potwierdzono rozpoznanie poprzez stwierdzenie obecności komórek nowotworowych w badaniu cytologicznym płynu mózgowo-rdzeniowego. U 72% pacjentek obserwowano także podwyższony poziom białka. Leczenie składało się z dokanałowo podawanego raz w tygodniu metotreksatu – 10 mg i Dx – 4 mg.

*Wyniki.* Kliniczną odpowiedź na leczenie oraz poprawę parametrów laboratoryjnych stwierdziliśmy u około 72% pacjentek. *Podsumowanie.* Nasze obserwacje wskazują, że najważniejszymi korzystnymi czynnikami rokowniczymi w przerzutach do opon mózgowo-rdzeniowych u chorych z rakiem piersi są: jednoczesne leczenie systemowe, dobry stan ogólny chorych w momencie rozpoznania, dobra odpowiedź kliniczna na leczenie metotreksatem, stwierdzona po 2 cyklach leczenia.

**Key words:** metastatic breast cancer, carcinomatous meningitis, intrathecal treatment

**Słowa kluczowe:** uogólniony rak piersi, nowotworowe zapalenie opon mózgowo-rdzeniowych, leczenie dokanałowe

### Introduction

Carcinomatous meningitis is a debilitating and progressive complication of cancer that results from metastatic infiltration of the leptomeninges and the cerebrospinal fluid

(CSF) by cancer cells. Among all solid tumors, breast and lung cancers, melanoma, and gastrointestinal tract cancer most frequently metastasise to the leptomeninges [1, 2]. Carcinomatous meningitis occurs in 1 to 5% of patients with breast cancer [1, 2]. The growing incidence of neoplastic meningitis is thought to be due both to the longer survival of cancer patients seen with current systemic therapies and to enhanced clinical vigilance and improved diagnostic tests [3].

The most common symptoms include headache, changes in mental status, cranial nerve palsies, back or

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radicular pain, incontinence, lower motor neuron weakness and sensory abnormalities. By the time most patients are diagnosed, they have a combination of cranial nerve, cerebral, and spinal signs and symptoms [4].

Diagnosis of carcinomatous meningitis is based on the recognition of a combination of neurologic symptoms and signs, plus on the demonstration of tumor cells by cytology in the CSF [2, 3]. CSF pleocytosis and elevations in CSF protein are non-specific abnormalities that are consistent with, but not diagnostic of, carcinomatous meningitis. Significant reduction in CSF glucose is found only in malignant or infectious disorders of the leptomeninges [5].

Neuroimaging techniques including cranial and spinal computed tomography or contrast-enhanced magnetic resonance (MR) may therefore be needed, and a high index of suspicion may be required for prompt diagnosis [6].

Therapy for carcinomatous meningitis has evolved to include radiation therapy to symptomatic sites and to regions of bulk disease in combination with intrathecal chemotherapy. In breast cancer-related meningeal metastases methotrexate is the commonly used intrathecal agent [2-5].

The median survival of patients with carcinomatous meningitis without therapy is approximately 4 to 6 weeks [3]. With intrathecal methotrexate and radiotherapy median survival is less than 6 months [3].

We have performed a retrospective analysis of patients treated in our clinic to derive prognostic factors for the better treatment of future patients.

## Material and methods

We reviewed 25 consecutive cases of carcinomatous meningitis caused by breast cancer. The neurological symptoms, pre-treatment characteristics, i.e. clinical stage at breast cancer diagnosis, tumor characteristics, receptor status, sites of metastatic lesions, and the methods of carcinomatous meningitis treatment were analysed. Moreover, laboratory parameters such as the CSF exam were analysed, i.e. pleocytosis, protein and glucose levels.

Concentrations analysis as a statistical test for small groups was applied for the statistics.

The therapy of neoplastic meningitis includes radiation therapy to symptomatic sites and regions of bulky disease, combined with methotrexate intrathecal-therapy and concurrent treatment of the breast cancer with systemic chemo- or hormone- therapy. The intrathecal treatment consisted of injection of preservative-free methotrexate 10 mg, plus dexamethasone 4 mg, administered two or three times twice a week and, subsequently, weekly to a maximum of twelve doses, or until the CSF clears. The CSF exam was performed every week. Intrathecal chemotherapy was typically administered using the lumbar puncture [7].

The clinical and laboratory response to the first two doses of intrathecal methotrexate injection was also analysed as a prognostic factor.

The evaluation of responses was based on Grossman classification [8]. If progression in CSF exam, imaging studies or clinical examination was observed, progression of the disease was recognised.

## Results

### Patients Characteristics

Twenty-five women with carcinomatous meningitis were treated in our clinic between January 2000 and October 2001. The patients' characteristics are presented in Table I.

**Table I. Patients characteristics**

Number of patients	25
Age – mean / range	45 / 29–70
Karnofsky (%) – mean / range	50 / 40–80
Prior radical breast cancer treatment	15 (60%)
Median of the interval from breast cancer diagnosis	26 months (from 1/2 to 84)
Prior systemic treatment of the metastatic breast cancer	17 (68%)
Presence of metastatic lesions in another localization	19 (76%)
Hormonal receptors: + / - / unknown	2 (8%) / 14 / 9
Cancer cells in cerebrospinal fluid exam	100%

The mean age at the time of diagnosis of carcinomatous meningitis was 46 years (range 29–70) and the median Karnofsky status was 50% (range 40–80%).

Five patients out of the 6 with Karnofsky status of 70 or 80% survived more than 6 months, while only 3 patients out of the 19 with Karnofsky of 40–60% achieved similar survival. Median overall survival for these two groups was 15,8 and 8,6 weeks, respectively.

The mean time from breast cancer diagnosis was 26 months (range from 1/2 to 84 months). Fourteen patients were hormonal receptors (HR) negative (56%), in 9 cases the hormonal status was unknown (36%). Only 2 patients were HR positive (8%).

In 15 cases (60%) previous radical treatment of breast cancer was performed. Seventeen (68%) women were previously treated with systemic chemotherapy as metastatic setting.

Other metastatic sites were associated with carcinomatous meningitis in 19 (76%) patients.

In one case the diagnosis of carcinomatous meningitis was established in pregnancy (28 weeks of gestation).

Clinical signs and symptoms of carcinomatous meningitis are presented in Table II. In most of the cases several symptoms were observed.

**Table II. Clinical signs and symptoms**

Symptoms	% of patients
Headache	85%
Vomiting / nausea	40%
Confusion	30%
Cerebellar syndrome	25%
Paresis /-plegia	25%
Pain of the thoraco-lumbar region	10%

Cancer cells in cerebrospinal fluid were detected in 100% of cases. Abnormal pleocytosis (normal range: 8 cells in field of vision) in CSF was detected in 24 patients (96%) in initial lumbar puncture. Increase of pleocytosis in consecutive lumbar punctures was evidence of disease progression and was strictly related to clinical status deterioration. (Figure 1) Cerebrospinal fluid protein (normal level: 45mg%) level was elevated in 18 cases (72%) (Figure 2). Decreased glucose level (normal level: 1/2 of serum level) in CSF at the time of diagnosis was observed in almost 90% of patients (22 cases) (Figure 3).

### Treatment characteristics

The intrathecal therapy was performed in 24 patients (96%); 1 woman withdrew consent. The mean number of intrathecal treatment cycles was 6, (range 0-15 cycles). The treatment was terminated if progression of the disease was documented and these patients received palliative care. In the pregnant woman the intrathecal injections of methotrexate and systemic chemotherapy were interrupted for 5 weeks during the labour period. Eighteen patients (72%) received systemic chemotherapy together with intrathecal treatment and 2 patients (8%) – systemic hormonal treatment. Individual programmes of systemic treatment were used, because most of the patients received one or two chemotherapies as adjuvant or metastatic setting. In 4 cases a taxans-based program was given, 3 patients received anthracyclines. In other cases vinorelbine with 5-fluorouracil or cisplatin in monotherapy were used. One premenopausal patient received goserelin with systemic chemotherapy, while in another letrozol was used as systemic treatment. In 3 patients systemic treatment was not planned because of extremely poor clinical status and 2 other patients died before the onset of systemic treatment. Longer median overall survival was documented for patients who had received systemic therapy (18,7 vs 6,6 weeks). The whole brain radiotherapy (2000-3000 cGy/g in 5 or 10 fractions) was performed additionally in sixteen (64%) patients.

### Toxicity

Treatment-related toxicities can occur from administration of intrathecal and systemic chemotherapy and radiation to symptomatic areas of the central nervous system. The most significant toxicity associated with the treatment of carcinomatous meningitis is the development of dementia due to necrotizing leukoencephalopathy. We observed progressive dementia in three patients (12%), probably as a complication of treatment. Intrathecal methotrexate with systemic chemotherapy can cause mucositis and myelosuppression. In our observation grade 3 or 4 neutropenia occurred only in 3 patients (12%). In 6 patients (24%) grade 3 mucositis was documented. Thrombocytopenia or anaemia were not observed. Infectious complications of the lumbar puncture were not documented.

### Response and survival

The response was achieved in 18 patients (72%). In this group the reduction of clinical signs of carcinomatous meningitis i.e. headache, nausea/vomiting, confusion and other symptoms after 2-4 cycles of intrathecal treatment was observed. In 7 patients (28%) disease progression occurred during the treatment. The median overall survival was 16,2 weeks. Nine patients (36%) survived beyond 6 months (only those who received systemic chemotherapy). One patient survived 54 weeks.

### Discussion

Meningeal metastases are an uncommon, but serious, complication of advanced breast cancer. Prognosis in this localisation of the disease is extremely poor. Current treatment of carcinomatous meningitis offers palliation for many patients.

The median overall survival in our data was 16,2 weeks. Other authors have demonstrated similar results, i.e. 10-16 weeks [1, 3, 5, 9]. The toxicity of intrathecal treatment, particularly with radiotherapy, was high. The most common toxicity is necrotizing leukoencephalopathy. In our group in 12% of patients progressive dementia was observed, as is reported by other authors (9-17%) [3-5, 10].

Grossman [8] and Jayson [5] have shown that Karnofsky status is a very important prognostic factor in carcinomatous meningitis. Patients with Karnofsky status of 50 or below survived for about 8 weeks, and patients with Karnofsky status of 60 or more survived for 20-30 weeks. Our results have confirmed this observation.

Additionally, our observations suggest that systemic chemotherapy is also an important prognostic factor in carcinomatous meningitis.

In historical data systemic chemotherapy was not used in patients with carcinomatous meningitis [5, 8, 11], and this factor was not analysed. Our data suggests that the blood-brain barrier is disrupted when carcinomatous meningitis develops and systemic chemotherapy can be effective against meningeal metastases from chemosensitive breast cancer.

A majority of authors [2, 3, 5, 8] emphasise that clinical response (reduction of headache and other symptoms) after 2 weeks of the treatment is a very important prognostic factor. In our data the clinical response after the first 2-3 cycles of intrathecal infusion of methotrexate was also found to be an important prognostic factor.

Our observations suggest that the important prognostic factors in carcinomatous meningitis are: systemic chemotherapy, Karnofsky status at the time of carcinomatous meningitis diagnosis and clinical response after the first 2 cycles of intrathecal infusion of methotrexate.

In conclusion, progress in the treatment of neoplastic meningitis is rather slow. The analysis of prognostic factors shows that systemic treatment with new active neoplastic agents may improve the results of treatment of

patients with breast cancer-related carcinomatous meningitis.

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