Neoplastic Meningitis from Breast Cancer: Feasibility and Activity of Long-term Intrathecal Liposomal Ara-C Combined with Dose-dense Temozolomide

A-L. HOFFMANN¹, J-H. BUHK² and H. STRIK³

Departments of ¹Neurology and ²Neuroradiology, University Medicine Göttingen, Göttingen; ³Department of Neurology, University of Marburg, Marburg, Germany

Abstract. Background: Patients with neoplastic meningitis (NM) from breast cancer have a median survival of 4-8 months with specific treatment. Here, good tolerance and long-term stabilization with combined intrathecal liposomal cytarabine (Ara-C), which is probably the most promising drug for intrathecal chemotherapy to date, near-continuous temozolomide and radiotherapy is reported in two patients with leptomeningeal and solid central nervous system (CNS) metastases from breast cancer. Case Reports: A 42- and a 43-year-old female presented with NM and disseminated CNS metastases from human epidermal growth factor receptor type 2 (Her2)-positive breast cancer. After irradiation of the symptomatic sites, intrathecal liposomal Ara-C every 2-4 weeks was combined with temozolomide 100 mg/m² day 1-5/7. Cerebrospinal fluid (CSF) cytology and neurological symptoms improved in both patients and stabilized for several months. The patients survived 10 and 17 months after diagnosis of NM, without signs of neurological toxicity. Conclusion: Intensive treatment is complicated by extensive pre-treatment and the lack of active CNS-penetrating systemic drugs. The long-term results with up to 17 intrathecal injections of liposomal Ara-C show that this treatment regimen is feasible and well-tolerated. The stabilization of both patients indicates activity of this combined intrathecal and systemic regimen that is based on long-term exposure of the tumour cells to both Ara-C and temozolomide. The results need to be confirmed prospectively.

Since the introduction of trastuzumab, the survival of human epidermal growth factor receptor type 2 (Her2)-positive breast cancer patients has improved. The rate of central nervous system (CNS) involvement, however, is increasing. This may not only be caused by the longer survival with improved control of the systemic disease, but also because trastuzumab, an antibody of relatively large-molecular size, cannot penetrate the blood-brain barrier (1). CNS involvement, whether solid or in the cerebrospinal fluid (CSF), is a severe complication that usually occurs in late stages of the disease. Neoplastic meningitis (NM) typically presents with multifocal symptoms at multiple levels of the CNS. Symptoms often include headache, nausea, cranial nerve palsy, radicular symptoms or paraparesis (2, 3). Neurological impairment most often progresses very rapidly.

The prognosis of patients with CSF dissemination and solid CNS metastases from breast cancer is poor. Effective therapy is complicated by the intense pre-treatment and the lack of active CNS-penetrating systemic drugs. Without specific treatment, the median survival of NM from solid tumours is 4-6 weeks (4, 5). Intensive treatment results in a median overall survival of 4-8 months, depending on the histology and dissemination of the primary tumour, the clinical condition, and therapy schedule (6, 7). Breast cancer seems to be the solid neoplasm responding best to therapy (3, 8).

Since there is no standard therapy and the individual stage of the primary neoplasm and systemic metastases has to be considered, the treatment has to be individualized. Therapeutic modalities include intrathecal and systemic chemotherapy, radiotherapy and, in the case of increased intracranial pressure or for the placement of a ventricular reservoir, surgery (9).

The drugs most commonly used for intrathecal therapy are methotrexate, cytarabine (Ara-C) and thiopeta. These substances have a half-life of only a few hours within the CSF (10). Liposomal encapsulation of Ara-C (DepoCyte®) results in a sustained-release and prolongs the half-life of Ara-C within the CSF from 3.4 to 140 hours and maintains cytotoxic concentrations for at least 21 days (11), thus intrathecal
administration is required only every 2-4 weeks (12). Such prolonged exposure of tumor cells to chemotherapy may lead to improved efficacy (13, 14).

Due to the rare occurrence and the lack of prospective, randomized studies, the relevance of the treatment options, systemic and intrathecal chemotherapy is not yet well determined. Moreover, CSF involvement only rarely occurs in isolation, but is often associated with solid systemic and CNS metastasis. Even after successful therapy of CSF involvement, progression of solid metastases may lead to clinical deterioration and death. Therefore, reports on the value of the respective treatment modalities are difficult to consider. The value of each treatment option has to be evaluated in the context of the entire disease and the whole therapeutic concept (9).

Although intrathecal application of chemotherapy achieves the highest concentrations in the CSF and is cleared more slowly from the CSF space than after systemic application (15), its efficacy for neoplastic meningitis from solid neoplasms remains unclear. One possible factor reducing its effect is the limited diffusion into solid tumour manifestations lining the CSF spaces. Distant solid spinal or cerebral metastases cannot be reached by intrathecal chemotherapy, although CNS metastases often coexist and also require treatment. Therefore, combined intrathecal and systemic chemotherapy may be the most promising regimen (13).

The majority of systemically applied drugs for the treatment of metastatic breast cancer, including trastuzumab, do not cross the blood-brain barrier. Temozolomide, an orally available alkylating agent with favorable toxicity profile, is effective against malignant gliomas and melanomas. Since it penetrates the blood-brain barrier, it seems to be an attractive agent to treat cerebral metastases. Only single reports exist on the use of temozolomide in breast cancer, either with conventional chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), an axillary relapse was operated in 2002. A 42-year old patient was diagnosed with Her2-positive breast cancer in 1994. After surgery and 6 cycles of chemotherapy with cyclophosphamide, methotrexate and 5-fluoruracil (CMF), an axillary relapse was operated in 2002. From January 2003 to May 2006, tamoxifen and gosereline (Zoladex®) were administered. 1 cycle of paclitaxel (Taxol®) was given and from June 2006, she received trastuzumab. In July 2006, metastases to the cervical spine were stabilized operatively and irradiated.

In January 2007, she developed severe headache, loss of vision of the right eye and suffered from numbness of the tongue and lumbar pain. MRI revealed extensive solid metastasis to the whole spinal cord and cerebellum and a slightly elevated CSF cell count with numerous malignant cells.

After irradiation to the whole brain and to the symptomatic lesions Th11 to S3, near-continuous systemic chemotherapy with temozolomide 100 mg/m² day 1-5/7 and lumbar intrathecal injections of liposomal Ara-C were initiated, every 14 days for 3 months and subsequently every 28 days under protection against arachnitis by oral dexamethasone 3x4 mg for 5 days. With this regimen, the headache, numbness of the tongue and lumbar pain improved markedly and remained stable. In June 2007, the CSF cell count had fallen from 6 to 0 cells/μL, the cerebellar metastases had regressed by approximately 50%, and the spinal metastases remained stable.

In August 2007, a slight ataxia developed that was caused by progression of a pre-existing intramedullar metastasis at level Th10, outside of the former radiation field. At the same time, a ventricular reservoir was implanted because of a newly occurring hydrocephalus. Unfortunately, the chemotherapy and spinal radiation had to be delayed for several weeks because of infection of the reservoir. Subsequently, the neurological status deteriorated and the patient developed paraparesis. In September 2007, control MRI showed progression of the cerebellar metastases and new supratentorial lesions. The patient died in December 2007 from tumour progression, 9.5 months after diagnosis of NM.

**Case 2. A 42-year old patient was diagnosed with Her2-positive breast cancer in 1994. After surgery and 6 cycles of chemotherapy with cyclophosphamide, methotrexate and 5-fluoruracil (CMF), an axillary relapse was operated in 2002. Subsequently, she received 6 cycles of paclitaxel (Taxol®), and regular trastuzumab was started. From April 2005, she received gosereline (Zoladex®) regularly. In December 2005, a relapse at the left brachial plexus was irradiated with 30 Gy. From February to December 2005, vinorelbine chemotherapy was administered.

In December 2006, the patient developed bladder dysfunction and a slowly progressing paraparesis. The diagnostic workup revealed diffuse solid spinal metastases and CSF involvement with 36 cells/μL, among them numerous tumour cells (Figure 1).

In March 2007, focal irradiation Th 10/11 with 30 Gy was applied, followed by near-continuous temozolomide 100 mg/m² day 1-5/7 and liposomal Ara-C every other week for 8

**Case Reports**

**Case 1. A 43-year-old woman suffering from Her2-positive breast cancer since March 2001 received 4 cycles AC-chemotherapy from April to July that year. A local relapse was surgically treated in October 2002. From January 2003 to May 2006, tamoxifen and gosereline (Zoladex®) were administered.**

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Due to the rare occurrence and the lack of prospective, randomized studies, the relevance of the treatment options, systemic and intra-CSF chemotherapy and radiotherapy, is not yet well determined. Moreover, CSF involvement only rarely occurs in isolation, but is often associated with solid systemic and CNS metastasis. Even after successful therapy of CSF involvement, progression of solid metastases may lead to clinical deterioration and death. Therefore, reports on the value of the respective treatment modalities are difficult to consider. The value of each treatment option has to be evaluated in the context of the entire disease and the whole therapeutic concept (9).

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In March 2007, focal irradiation Th 10/11 with 30 Gy was applied, followed by near-continuous temozolomide 100 mg/m² day 1-5/7 and liposomal Ara-C every other week for 8
weeks and then every 4 weeks under protection against arachnitis by oral dexamethasone 3×4 mg for 5 days. The bladder dysfunction improved to normal function and the paraparesis stabilized with only a slight paresis of the left leg remaining. MRI showed stable spinal metastases in June 2007. The CSF cell count dropped to normal values and the CSF was free of tumour cells one single time in August 2007 (Figure 1).

In November 2007, MRI showed progression of a pre-existing metastasis Th 5/7. Despite rapid irradiation, the patient developed subtotal paraparesis. In December 2007, a combination of oral capecitabine and lapatinib was initiated, but had to be stopped after 1.5 cycles because of severe, uncontrollable diarrhoea. The CSF, however, was free of tumor cells one more time in February 2008. Temozolomide was started again as a palliative chemotherapy and the combination with liposomal Ara-C continued, because of persistance of malignant CSF cells, until June 2008. Because of infected gluteal ulcerations and deterioration of the general status, liposomal Ara-C was stopped after the 17th application and temozolomide after a total of 14 months of near-continuous application. In spite of intensive care of the skin ulcerations, the patient died in July 2008 from septicaemia without signs of progression of the CNS manifestation, 16.8 months after diagnosis of NM.

Discussion

Opinions on the value of the different treatment schedules in NM are contradictory. Radiotherapy may alleviate neurological symptoms, but is not associated with a longer survival (7). Several authors have reported good efficacy of systemic chemotherapy (21, 22). In approximately two thirds of cases, neoplastic meningitis occurs together with new or progressive systemic metastases and progression of the primary neoplasm (23). Consequently, up to half of the patients with NM die from systemic disease and not NM (22-24). The treatment of NM therefore has always to be planned as a whole concept that includes treatment of the CNS as well as the systemic disease. This is only guaranteed by systemic chemotherapy.

An intravenous application that also targets the CSF space requires much higher doses to achieve adequate CSF-concentrations than intrathecal injection. A combined treatment of systemic and CSF disease can be applied with high-dose intravenous methotrexate (HD-MTX), for which favorable results have been reported (25-27). The use of HD-MTX, however, is limited in patients with relevant comorbidity and a higher rate of systemic toxicity might be expected (13, 28). The efficacy of intrathecal chemotherapy remains unclear. Several reports in the literature suggested that it improves the outcome of patients with NM (29-33). Other groups found no additional effect on survival (6, 21).

In NM from solid tumours, cases of long-lasting cytological complete remission during treatment with intrathecal liposomal Ara-C have been reported (27). In randomized studies, a significantly longer time to neurological progression, but no significantly better survival, was observed with liposomal Ara-C as compared with MTX (34). This could not be confirmed in a subsequent study with both solid and haematological malignancies and different routes of application (35).

In CNS metastases from breast cancer, activity of conventionally applied temozolomide (200 mg/m² day 1-5/28) was limited (16-18). Only in one series was some efficacy seen (36). In recurrences of malignant gliomas, we have observed better responses with a near-continuous temozolomide regimen (100 mg/m² day 1-5/7) despite failure of conventionally applied temozolomide (20). Although the dose per cycle is doubled with the near-continuous regimen, good haematological tolerance was seen and dose adaptation was uncomplicated. Apart from tolerance, the near-continuous application aims at permanent depletion of O6-methyl-DNA-guanine-methyl transferase (MGMT), an important predictive factor in glioblastomas. In breast cancer, MGMT activity was found to be even higher than in glioma (37). We therefore also expected temozolomide to be effective in breast cancer patients through targeting MGMT by near-continuous application. Thus, temozolomide was applied in an altered, near-continuous schedule and aimed at stabilizing solid systemic and CNS metastases and at supporting the intra-CSF cytotoxicity of liposomal Ara-C.

The long-term treatment of both patients receiving this multimodality regimen without severe toxicity proved the feasibility of this strategy. Glas et al. reported application of 9 cycles of liposomal Ara-C in combination with whole-brain radiotherapy (WBRT) in a patient with NM from breast cancer without neurotoxicity (38).

Here the feasibility of up to 17 injections of liposomal Ara-C combined with systemic temozolomide after WBRT without detectable toxicity was demonstrated, supporting the potential of long-term combination of intrathecal and systemic therapy. Individual dose adaptation of systemic temozolomide also enables the application of such a therapy to patients with critical blood counts. With this concept, the need for high-dose systemic chemotherapy with the risk of severe side-effects can be avoided and therapy can also be given to patients that would not tolerate high-dose MTX due to renal or cardiac comorbidity.

The clinical improvement and stabilization was probably associated with both radiotherapy and combined systemic and intrathecal chemotherapy. Although radiotherapy is known to be of good efficacy for the improvement of symptoms, this treatment option alone is not expected to induce long-term stabilization (4, 22, 39). Both patients, however, had spinal relapses outside of the previous
radiation field, indicating a possible long-term effect of radiation when combined with chemotherapy. The overall stabilization of ≥6 months, however, would most probably not have been possible without systemic chemotherapy. The additional intrathecal chemotherapy, which normalized cell counts in both patients, was considered to be an integral part of the treatment concept to control the CSF tumour cells. With the use of liposomal Ara-C, the frequency of lumbar punctures only every 2-4 weeks is reduced to a tolerable level.

In conclusion, long-term stabilization or improvement in aggressively metastasizing breast cancer is possible with a multimodal treatment including near-continuous exposure of tumor cells to intrathecally and systemically applied chemotherapy. The results need to be confirmed prospectively.

References


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