VIA MEDICA
REVIEW ARTICLE

Anna Niwińska, Michał Kunkiel

Department of Breast Cancer and Reconstructive Surgery, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw

Leptomeningeal metastases in breast cancer patients — current rules of diagnosis and treatment

Address for correspondence:
Dr n. med. Anna Niwińska
Klinika Nowotworów Piersi
i Chirurgii Rekonstrukcyjnej
Centrum Onkologii — Instytut
im. M. Skłodowskiej-Curie w Warszawie
e-mail: annaniwinska@gmail.com

Oncology in Clinical Practice
2016, Vol. 12, No. 5, 179–184
DOI: 10.5603/OCP.2016.0010
Translation: lek. Maciej Kawecki

ISSN 2450–1654

ABSTRACT

Leptomeningeal metastases (LM) presents a challenge because of the difficulty in determining the diagnosis and lack of optimal therapy. Nowadays, LM are more frequently diagnosed as a consequence of the long survival of patients with breast cancer and the improvement in image analysis. LM is a deleterious complication of breast cancer leading to death of patients within less than 3–6 months from the diagnosis. No generally accepted standard of care in the treatment of breast cancer LM exists. The treatment of patients with breast cancer and LM is of limited efficacy and substantial toxicity. Usually it requires focal radiotherapy to symptomatic sites or areas of bulky disease, intra-cerebrospinal fluid chemotherapy, or systemic intravenous/oral therapy, but the data regarding the sequence and efficacy of particular types of treatment are disputable. The management of breast cancer patients with LM was reviewed based on the data from literature. Additionally, the results of randomised clinical trials were reviewed.

Key words: leptomeningeal metastasis, carcinomatous meningitis, intrathecal treatment, toxicity of treatment, breast cancer

Oncol Clin Pract 2016; 12, 5: 179–184

Introduction

Leptomeningeal metastases (LM) of solid tumours, in Polish literature also called *cancerous leptomeningitis*, comprises the presence of cancer cells in the subarachnoid cavity (in cerebrospinal fluid and/or in leptomeninges). In Anglo-Saxon terminology LM or *neoplastic meningitis* are used to describe cancerous involvement of leptomeninges that originate from different organs (lymphomas, gliomas, carcinomas, and malignant melanomas). Terms such as carcinomatous meningitis, meningeal carcinomatosis, or leptomeningeal carcinomatosis define the presence of carcinoma cells in leptomeninges (most commonly from breast cancer, small cell and non-small cell lung cancer, and gastrointestinal cancers).

The rate of diagnosis of leptomeningeal metastases is growing, mostly due to the prolonged survival of cancer patients and improved imaging. About 5–15% of patients with lymphoma or leukaemia and about 1–8% of patients with carcinoma develop LM [1–7].

The longest survivals of patients with leptomeningeal metastases are observed in breast cancer [1–3, 5, 8–11]. Nearly 60% of patients in this group respond to treatment, with responses lasting about 3–6 months (median 4 months) [5, 12–16]. However, only 10–15% of treated patients remain alive for over one year [3, 13, 14]. Patients without treatment, with unfavourable risk factors, survive only 4–6 weeks [6]. Metastases in different organs are found simultaneously in 70–90% of patients [4–6, 17, 18], with parenchymal brain metastases in nearly 50% of them [1, 4, 18]. Breast cancer subtypes with the highest rates of LM are triple-negative breast cancers and, among histological subtypes, lobular carcinoma [13].

Currently, no strict guidelines for a therapeutic approach in LM of breast cancer exist. Only a few randomised clinical trials have addressed this matter (most of them regarding intrathecal drug administration), and most of them included different cancer types, with breast cancer cohorts limited to 35 patients at best. No single

treatment response criterion has been established yet because changes observed in radiological imaging and in cerebrospinal fluid analyses do not always correlate with clinical response and performance status [11, 18–20].

In this review, we present up-to-date data about the pathophysiology, clinical symptoms, diagnosis, and treatment of leptomeningeal metastases of breast cancer.

Pathophysiology

The subarachnoideal cavity, which separates the arachnoid mater and pia mater, contains approximately 140 ml of cerebrospinal fluid, a volume that is similar in every person. The amount of fluid produced daily is estimated to be 600–800 ml, and given the constant reabsorption, the whole volume of cerebrospinal fluid is exchanged several times per day [4, 5]. Cancer cells that enter the cerebrospinal fluid usually relocate gravitationally to the posterior cranial fossa and the lumbosacral part of the spinal canal [5]. In the next stage, they infiltrate the surface of brain, cranial nerves, spinal cord, and spinal nerves roots [3, 6, 21]. Metastases may grow as a diffused infiltration along meninges or may form nodes (most often in posteriori cranial fossa and in cauda equina). The presence of neoplastic growth in meninges often results in a diversified degree of local inflammation [1]. Cerebral fluid examination usually reveals pleocytosis (stimulated lymphocytes and monocytes) [4, 6]. Fibrosis limits cancer growth but also leads to a narrowing of blood vessels, local ischaemia, altered neural metabolism, and permanent nerve damage [4, 22].

Clinical signs

Clinical signs of leptomeningeal metastases are usually an effect of pressure and infiltration of neural tissue in the following: 1) cerebrum and cerebellum, 2) spinal cord, 3) cranial nerves, and 4) spinal nerves roots. Implantation of cancer cells in different parts of the subarachnoid cavity results in simultaneous occurrence of multifocal neurological defects [1–6, 11, 18–20]. Signs from cerebrum and cerebellum include strong headache, nausea, vomiting, memory impairment, changes in personality, altered mental states, drowsiness, signs of meningeal irritation, and coma. Nerve dysfunction affects most often III, IV, VI, and VII cranial nerves, but every nerve, even II and VIII, might be involved. Metastases in spinal cord may induce signs such as radicular pain (usually in a lumbar area of the vertebrae and in the back of the neck), paraesthesia and pain in limbs, muscle weakness, and faecal and urinary incontinence [2–6, 13–15, 19].

Diagnosis

Diagnosis of leptomeningeal metastases relies on confirmation of a triad of signs ("gold standard") that include:

— clinical presentation of a number of different neurological syndromes that occur with different intensity;
— abnormal results of cerebrospinal fluid, which include the presence of cancer cells, polycytosis, increased protein, and decreased glucose concentration;
— the presence of metastases in magnetic resonance imaging (MRI).

The most important test that confirms diagnosis of LM is the detection of cancer cells in the cerebrospinal fluid [1–5, 11, 19, 20]. However, diagnosis cannot be excluded even in absence of the triad presented above. Evidence of the existence of cancer cells in the cerebrospinal fluid with the presence of neurological signs with normal MRI results, as well as the presence of neurological signs with a meningeal infiltration detected in MRI without cancer cells in cerebrospinal fluid, are sufficient to confirm the diagnosis. However, it should be emphasised that the presence of neurological symptoms with atypical cytosis without evidence of cancer cells in the cerebrospinal are insufficient to confirm diagnosis and foreclose eventual treatment. The probability of LM in such situations is significant, but not certain, and justifies repetition of lumbar puncture and MRI [11].

Recent studies have tried to assess the value of testing EpCAM (epithelial cell adhesion molecule) concentration in cerebrospinal fluid as a marker of LM, especially in cases with absence of cancer cells [23, 24].

The most effective method of radiological imaging in case of LM suspicion is magnetic resonance imaging with contrast. It allows detection of changes such as a linear meningeal infiltration, nodule formation in pia mater, hydrocephalus, and nerves thickening [2–5].

Prognostic factors

An adequate assessment of prognostic factors in LM allows the selection of subgroups of patients with a favourable prognosis, who could benefit from intensified oncological treatment (despite palliative setting), and patients with an unfavourable prognosis, who would only need best supportive care.

Patients with a poor performance status — with a vast nervous system infiltration that results in encephalopathy, with disturbances in the cerebrospinal fluid circulation, with major neurological defects, or with an uncontrolled systemic involvement of different organs (metastases in several parenchymal organs) — have poor prognosis and should receive only best supportive care

or treatment limited to the radiotherapy of sites responsible for neurological symptoms. In contrast, patients with adequate performance status — with limited LM, without major neurological defects, with maintained cerebrospinal fluid circulation, with a controlled or potentially controlled metastases in other organs, and with a probability of survival over three months — should be treated with available oncological modalities with the aim of prolonging survival and improving quality of life [1, 3, 5, 6, 8, 9, 20, 25–27].

The most important prognostic factor that determines overall survival and treatment effectiveness is the patient's performance status [8, 13, 14, 28].

Treatment

According to the *USA National Comprehensive Cancer Network* (USA NCCN), patients with an unfavourable prognostic factors should receive best supportive care (corticosteroids and/or analgesic drugs, antidepressants, anxiolytics, and anticonvulsants) and — whenever appropriate — radiotherapy of the areas causing symptoms [27]. In patients with significantly increased intracranial pressure, implantation of a ventriculo-peritoneal shunt should be considered as a supportive treatment.

Treatment modalities for patients with favourable prognostic factors include radiotherapy, cytotoxic drugs administered to the subarachnoideal cavity (intrathecal chemotherapy), and/or systemic treatment (chemotherapy, hormonal therapy, targeted therapy). Therapy aims at improving quality of life by mitigation of neurological symptoms and pain reduction, and at prolonging survival [1–4, 19]. Currently, no standard treatment sequence exists [3, 18–20, 29], especially among heavily pretreated patients, in whom selection of active therapy with an acceptable toxicity profile might be problematic. According to the USA NCCN, in patients with favourable prognostic factors, recommended proceedings include cerebrospinal fluid circulation assessment, with sequential provision of radiotherapy for the areas that restrict circulation, and then subsequent administration of intrathecal or systemic treatment [27]. However, this approach is not commonly recognised as a standard. Different approaches include beginning the therapy with intrathecal administration of cytotoxic drugs if numerous cancer cells are found in cerebrospinal fluid analysis, as a way to improve cerebrospinal fluid circulation by decreasing the fluid stickiness. Also, in the case of numerous nodular metastases, significant meningeal infiltration (with a profound pathological vascularisation), or uncontrolled metastases in different organs, systemic treatment should be considered as a primary treatment modality [7, 30]. The decision about treatment sequence and its further modifications should be taken by an experienced interdisciplinary team.

Radiotherapy

The most common indications for radiotherapy include: presence of neurological symptoms, existence of a vast cancerous infiltration of the meninges, and changes that restrict cerebrospinal fluid circulation [1–6, 8, 9, 12, 25, 26, 31]. A total dose of 30 Gy in 10 daily fractions of 3 Gy is usually given [1, 4, 5, 32–34]. However, no randomised controlled trial regarding the effectiveness of the radiotherapy in LM has yet been undertaken.

Intrathecal therapy

One of the most controversial areas of LM treatment is intrathecal administration of cytotoxic drugs. In the majority of studies, no effect on survival prolongation was shown, with responses limited to the mitigation of symptoms and an improvement in neurological status. Frequent and severe side effects related to the intrathecal drug administration significantly limit its application.

Currently available drugs used for the intrathecal administration are methotrexate, thiotepa, and cytosine arabinoside, called also cytarabine, in a conventional or liposomal formulation. Routes of administration include lumbar puncture (intrathecal administration) and delivery to lateral ventricles of the brain by an implanted subcutaneous Ommay or Rickham reservoir (intraventricular administration) [4, 7]. Intraventricular administration is more convenient for the patient and is better tolerated but may be linked to some severe side effects such as intraventricular bleeding or central nervous system infection [35–37].

Thus far, only six randomised clinical trials regarding leptomeningeal metastases from solid tumours or lymphomas have been performed [26, 38–42]. All of them included intrathecal drug administration. Only five of six trials included breast cancer patients (with a total number of 129 breast cancer patients in all trials), and only one trial was dedicated only to such patients [41]. Cohorts included in the studies numbered from 28 to 103 patients. Trials compared effectiveness between different single drugs administered intrathecally, or between a single drug and a two drug combination. In solid tumours a two-drug combination was not superior to a one-drug intrathecal therapy, and no single drug was significantly superior to others. However, in the treatment of lymphomas, liposomal cytarabine was shown to be more effective than methotrexate. In all of the discussed randomised controlled trials mean survival of the breast cancer patients treated intrathecally was 15 weeks [43].

A randomised clinical trial by Glantz et al. [40] compared the effectiveness of methotrexate and li-

posomal cytarabine in 61 patients with LM from solid tumours (including 22 patients with breast cancer). Both methotrexate and liposomal cytarabine induced similar response rates — 26% and 20% (p = 0.76), respectively — and comparable median overall survival of appropriately 105 and 78 days, respectively (p = 0.15). Nevertheless, a statistically significant longer time to neurological progression was observed in the arm with liposomal cytarabine (58 days *vs.* 30 days; p = 0.007). Rates of drug-induced meningitis were similar between compared arms (23% after liposomal cytarabine and 19% after methotrexate, p = 0.57). An additional advantage of liposomal cytarabine was administration at longer intervals (six cytarabine administration equalled 16 administrations of methotrexate).

A randomised clinical trial by Boogerd et al. included 35 breast cancer patients with LM [41]. The aim of the study was to assess value of an intraventricular treatment. In the first arm the patients received radiotherapy and systemic treatment only, and in the second arm patients additionally received intraventricular treatment with methotrexate. The addition of intraventricular treatment did not improve patients' survival and significantly increased toxicity rates. Median progression free survival was 23 weeks in the arm with intraventricular methotrexate and 24 weeks in the arm without. Median survival was 18 weeks in the group receiving methotrexate and 30 weeks (p = 0.32) in the arm without intraventricular treatment. Nearly 47% patients in the methotrexate arm group experienced side effects, such as headaches, impaired consciousness, drug-induced meningitis, infection, and leukoencephalopathy if the cumulative drug dose reached 150–170 mg. The adverse event rate in the arm without intraventricular treatment reached 6% (p = 0.007). On the basis of the presented data, the authors concluded that in breast cancer patients with LM a combination of systemic therapy and radiotherapy is the primary treatment option, and that the addition of intraventricular chemotherapy is dispensable.

In our retrospective study, based on a cohort of 149 patients with breast cancer and leptomeningeal metastases, we compared outcomes and effectiveness of intrathecal methotrexate and liposomal cytarabine [14]. No significant differences between methotrexate and liposomal cytarabine were seen in terms of effectiveness (median overall survival 4.2 *vs.* 4.6 months (p = 0.546), respectively). However, liposomal cytarabine usage was more convenient due to longer intervals between drug administrations. Liposomal cytarabine should be considered a treatment of choice in patients with impaired mobility because of neurological symptoms and in patients living at a significant distance from a treatment centre (fewer hospital visits). The major disadvantage of liposomal cytarabine, when compared to methotrexate, is its higher treatment costs.

Cytotoxic drugs administered to the subarachnoid cavity often induce severe adverse events. Early and late toxicities might be distinguished. In 10–25% of patients acute, drug-induced, aseptic meningitis occurs [7]. Usually symptoms begin within a few hours after drug administration. The diagnosis requires the occurrence of stiffness and pain in the neck and another two symptoms from the following: headache, nausea, vomiting, pain in the back, fever, impaired consciousness, coma, pleocytosis in a cerebrospinal fluid analysis without the presence of cancer cells, and negative cerebrospinal fluid cultures [6, 7, 11, 38, 40]. Treatment includes corticosteroids and nonsteroidal anti-inflammatory drugs. Normally, symptoms resolve within three days [7]. The rate of occurrence of drug-induced meningitis after administration of liposomal cytarabine, which typically presents as cauda equina or conus medullaris syndrome, is estimated at about 17% [7]. In such cases intravenous corticosteroid treatment should be introduced.

The most common late adverse event, which may arise in 10–25% of patients receiving intrathecal treatment, is leukoencephalopathy [1–3, 5–7, 25, 44, 45]. Clinical symptoms include progressive and irreversible decrepitude with cognitive function impairment, focal neurological signs, bowel and urinary constrictor dysfunction, and seizures. In T2-weighted magnetic resonance imaging, hyperintense changes in periventricular white matter can be detected [41].

Systemic treatment

Most of the patients diagnosed with LM also have metastases in different organs and therefore require systemic therapy. Until recently, systemic treatment was considered ineffective in cases of leptomeningeal metastases, due to the robustness of the blood-brain barrier. However, cancer cell infiltration disrupts the blood-brain barrier and, along with pathological vascularisation created by metastases growing in meninges, provides an opportunity for drugs to diffuse from the blood to the cerebrospinal fluid in the subarachnoideal cavity.

Several studies, mostly published after 2004, provide evidence for the activity of systemic therapy administered intravenously and orally in the management of patients with LM, and is the only treatment modality that showed prolongation of patients' survival [13–16, 28, 41, 45–47]. Our previous reports showed that even though intrathecal therapy and radiotherapy play an important role in enhancing patients' quality of life, only systemic therapy provides a statistically significant improvement in overall survival [13, 14].

The role of hormonal therapy in breast cancer patients with LM is uncertain, although tamoxifen and aromatase inhibitors can cross the blood-brain barrier, and a single study reports neurological and cytological improvement after hormonal therapy [48].

Novel therapies

Several ongoing studies are evaluating the effectiveness of non-standard drugs administered intrathecally, including mafosfamide, nitrosourea, gemcitabine, etoposide, topotecan, trastuzumab, rituximab, and interferon α. Various intravenous drugs, not yet evaluated in the setting of breast cancer leptomeningeal metastases, are under investigation (nitrosourea, etoposide, liposomal doxorubicin, interleukin-2, gefitinib, erlotinib, vemurafenib, dabrafenib, rituximab, and trastuzumab) [1, 4, 7, 46, 47].

Significant hope is placed in trastuzumab administered into the subarachnoideal cavity. No randomised clinical trial of intrathecal trastuzumab has been carried out, but several case reports and the analysis of a cohort of 17 patients have been published [47]. In the presented cases, trastuzumab was administered intrathecally in different schemes and in various doses (ranging from 4 mg to 150 mg). In some of the cases it was combined with intrathecal methotrexate or liposomal cytarabine, and in others concurrent systemic therapy was used (with trastuzumab, paclitaxel, capecitabine, cisplatin, etoposide, or doxorubicin). A clinical improvement was obtained in 68% of cases, and a regression in cerebrospinal fluid analysis was seen in 66% of patients. Achieved responses did not translate into improved overall survival, but they had an influence on the prolongation of the time to neurological progression. The authors of the cohort analysis concluded that trastuzumab, used alone or in combination with different drugs, is a safe option of palliative treatment, which leads to clinical improvement in some patients [47]. However, the small number of analysed patients, selection bias regarding reported cases, and several cases of combination therapy with intrathecal and systematic treatment make evaluation of trastuzumab in this setting impossible. Moreover, the therapy effects were limited to a palliation of symptoms, and no gain in survival was observed. There remains the need for a randomised clinical trial in order to fully evaluate the effectiveness of trastuzumab administered intrathecally in breast cancer patients with leptomeningeal metastases.

Problems to solve

The limited effectiveness and high toxicity of the currently used treatment for LM justifies further studies regarding optimal treatment schedules and reliable ways of assessing treatment responses. Several problems await resolution.

Firstly, it not yet known whether intrathecal/intraventricular treatment in breast cancer patients with LM is as effective as in cancers originating from the lymphatic system and whether it should be routinely used, considering its substantial toxicity and probable limited effect on overall survival.

Secondly, if we consider intrathecal/intraventricular treatment only as way of palliating symptoms, toxicity assessment is a priority. Nevertheless, published studies often lack data regarding the side effects associated with the treatment.

Thirdly, despite the proven value of systemic treatment in breast cancer LM, its optimal place in a sequence with radiotherapy and intrathecal therapy is not yet determined.

Fourthly, clinical trials have shown that, at present, there is no effective way of assessing treatment response in patients with leptomeningeal metastases. Complete cytological response (disappearance of cancer cells form cerebrospinal fluid) has no effect on prolongation of patients' survival. Overall survival depends more on the neurological rather than cytological response, despite the difficulties in evaluating neurological responses. Without standardisation of neurological examination, we lack a strict and accurate method of assessing progression or regression of the disease [24]. Radiological imaging also has limited effectiveness, as the extensity of changes determined in MRI does not correlate with the neurological state or performance status of patients. Paradoxically, treatment effects seen as an improvement in patients' symptoms might occur even without any regression seen in radiological imaging.

The problems presented above forced the group of experts in the field of leptomeningeal metastases (International Panel of Experts US and Europe The RANO Group — Response Assessment in Neuro-Oncology) to critically analyse available data from randomised clinical trials and to draw possible long-term strategies for improvement in diagnostic, treatment, and response evaluation in patients with LM from solid tumours [18]. It seems that overall survival rates at 6 and 12 months are the most objective points for assessing treatment effectiveness and for comparing different groups with LM [43].

Conclusions

Currently, no strict guidelines for the therapy of breast cancer patients with leptomeningeal metastases exist. Systemic chemotherapy is the only therapeutic modality that significantly prolongs survival and allows control of metastases in locations other than meningeal. Intrathecal therapy and radiotherapy seem to not extend survival, but they can improve quality of life and therefore are a vital part of palliative treatment. Due to disappointing effects of LM treatment, there is an urgent need for a standardisation of response evaluation and implementation of new therapies originating from good quality randomised clinical trials.

References

1. Jayson GC, Howell A. Carcinomatous meningitis in solid tumours. Ann Oncol 1996; 7: 773–786.
2. Steinfeld AD. Radiation therapy. In: Roses DF (ed.). Breast Cancer, Churchill Livingstone, Philadelphia 1999: 570–572.
3. Johnson KA, Kramer BS, Crane JM. Management of central nervous system metastases in breast cancer. In: Bland KI, Copeland EM (ed.).The Breast. Comprehensive management of benign and malignant diseases (ed. 2). WB Saunders Company Philadelphia 1998: 1389–1402.
4. De Angelis LM, Rogers LR, Foley KM. Leptomeningeal metastasis. In: Harris JR, Lippman ME, Morrow M, Osborne CK (ed.). Diseases of the breast (ed. 2). Lippincott Wiliams & Wilkins, Philadelphia 2000: 867–874.
5. Grossman SA. Advances in the treatment of central nervous system metastases: treatment of neoplastic meningitis. American Society of Clinical Oncology Proceedings , 37-th Annual Meeting, May 12–15 2001, San Francisco, California 2001: 598–604.
6. .Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastasis from solid tumours: experience with 90 patients. Cancer 1982; 49: 759–772.
7. Mack F, Baumert BG, Schafer N et al. Therapy of leptomeningeal metastasis in solid tumors. Cancer Treat Rev 2016; 43: 83–91.
8. Jayson GC, Howell A, Harris M, Morgenstern G, Chang J, Ryder WD. Carcinomatous meningitis in breast cancer: an aggressive disease variant. Cancer 1994; 74: 3135–3141.
9. Fisazi K, Asselain B, Vincent-Salomon A et al. Meningeal carcinomatosis in patients with breast carcinoma. Cancer 1996; 77: 1315–1323.
10. Giannone L, Greco FA, Hainsworth JD. Combination intraventricular chemotherapy for meningeal neoplasia. J Clin Oncol 1986; 4: 68–73.
11. Scott BJ, Kesari S. Leptomeningeal metastases in breast cancer. Am J Cancer Res 2013; 3: 117–126.
12. Yap H, Yap B, Rasmussen S et al. Treatment for meningeal carcinomatosis in breast cancer. Cancer 1982; 49: 219–222.
13. Niwińska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: propensity of breast cancer subtypes for leptomeninges and the analysis of factors influencing survival. Med Oncol 2013; 30: 408–415.
14. Niwińska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: the results of combined treatment and the comparison of methotrexate and liposomal cytarabine as intra-cerebrospinal fluid chemotherapy. Clin Breast Cancer 2015; 15: 66–72.
15. Rudnicka H, Niwińska A, Murawska M. Breast cancer leptomeningeal metastasis-the role of multimodality treatment. J Neurooncol 2007; 84: 57–62.
16. Jo JCh., Kang MJ, Kim JE et al. Clinical features and outcome of leptomeningeal metastasis in patients with breast cancer: a single center experience. Cancer Chemother Pharmacol 2013; 72: 201–207.
17. Grossman SA, Moynihan TJ. Neurologic complication of systemic cancer: neoplastic meningitis. Neurol Clin 1991; 9: 843–856.
18. Chamberlain M, Soffietti R, Raizer J et al. Leptomeningeal metastasis: a response assessment in neuro-oncology critical review of endpoints and response criteria of published randomized clinical trials. Neuro--Oncol 2014; 16: 1176–1185.
19. Chamberlain MC. Leptomeningeal metastasis. Curr Opin Oncol 2010; 22: 627–635.
20. Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: leptomeningeal metastases in solid tumours. Surg Neurol Int 2013; 4: S265–288.
21. Gonzalez-Vitale JC, Garcia-Bunuel R. Meningeal carcinomatosis. Cancer 1976; 37: 2906–2911.
22. Klein P, Haley C, Wooten F, VandenBerg SR. Focal cerebral infarctions associated with perivascular tumour infiltrates in carcinomatous leptomeningeal metastases. Arch Neurol 1989; 46: 1149–1152.
23. Subira D, Simo M, Illan J et al. Diagnostic and prognostic significance of flow cytometry immunophenotyping in patients with leptomeningeal carcinomathosis. Clin Exp Metastasis 2015; 32: 383–391.
24. Chamberlain MC, Johnston SK. Neoplastic meningitis: survival as a function of cerebrospinal fluid cytology. Cancer 2009; 115: 1941–1946.
25. Boogerd W, Hart AA, van der Sande JJ, Engelsman E. Meningeal carcinomatosis in breast cancer. Prognostic factors and influence of treatment. Cancer 1991; 76: 1685–1695.
26. Grossman SA, Finkelstein DM, Ruckdeschel DL et al. Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. J Clin Oncol 1993; 11: 561–569.
27. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Central Nervous System Cancer. Version 2. 2013.
28. Du CH, Hong R, Shi Y, Yu X, Wang J. Leptomeningeal metastasis from solid tumors: a single center experience in Chinese patients. J Neurooncol 2013; 115: 285–291.
29. Kak M, Nanda R, Ramsdale EE, Lucas RV. Treatment of leptomeningeal carcinomatosis: Current challenges and new opportunities. J Clin Neurosc 2015; 22: 632–637.
30. Fisher R, De Angelis LM. Leptomeningeal metastasis. In: Harris JR, Morrow M, Lippman ME, Osborne CK (ed.). Disease of the Breast (ed. 4). Lippincott Williams & Wilkins, Philadelphia 2010: 1001–1007.
31. Ongerboer de Visser BW, Somers R et al. Intraventricular methotrexate therapy of leptomeningeal metastasis from breast cancer. Neurology 1983; 33: 1565–1572.
32. Chamberlain MC, Corey-Bloom J. Leptomeningeal metastases: 111 Indium-DTPA CSF flow studies. Neurology 1991; 41: 1765–1769.
33. Grossman SA, Trump DL, Chen DCP, Thompson G, Camargo EE. Cerebrospinal fluid flow abnormalities in patients with neoplastic meningitis: An evaluation using 111-indium-DTPA ventriculography. Am J Med 1982; 73: 641–647.
34. Glantz MJ, Hall WA, Cole BF et al. Diagnosis, management of and survival of patients with leptomeningeal cancer based on cerebrospinal fluid-flow status. Cancer 1995; 75: 2919–2931.
35. Pardo-Moreno J, Fernandez C, Arroyo R et al. Safety of intra-cerebrospinal fluid chemotherapy in oncohematological patients: a retrospective analysis of 627 interventions. J Neurooncol 2015; 125: 351–358.
36. Zairi F, Le Rhun E, Bertrand N et al. Complications related to the use of an intraventricular access device for the treatment of leptomeningeal metastases from solid tumoo: a single centre experience in 112 patients. J Neurooncol 2015; 124: 317–323.
37. Roguski M, Rughani A, Lin ChT et al. Survival following Ommaya reservoir pa cement for neoplastic meningitis. J Clin Neurosc 2015; 22: 1467–1472.
38. Hitchins RN, Bell DR, Woods RL, Levi JA. A prospective randomized trial of single agent versus combination chemiotherapy in meningeal carcinomatosis. J Clin Oncol 1987; 5: 1655–1662.
39. Glantz MJ, LaFollette S, Jaeckle KA et al. Randomized trial of a slow release versus a standard formulation of cytarabine for the intrathecal treatment of lymphomatous meningitis. J Clin Oncol 1999; 17: 3110–3116.
40. Glantz MJ, Jaeckle KA, Chamberlain MC et al. A randomized controlled trial comparing intrathecal sustained-release cytarabine (DepoCyt) to intrathecal methotrexate in patients with neoplastic meningitis from solid tumors. Clin Cancer Res 1999; 5: 3394–3402.
41. Boogerd W, van den Bent MJ, Koehler PJ et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: a randomized study. Eur J Cancer 2004; 40: 2726–2733.
42. Shapiro WR, Schmid M, Glantz M et al. A randomized phase III/IV study to determine benefit and safety of cytarabine liposome injection for treatment of neoplstic meningitis. J Clin Oncol 2006; 24 (suppl): 1528s.
43. Scott BJ, Oberheim-Bush NA, Kesari S. Leptomeningeal metastasis in breast cancer — a systematic review. Oncotarget 2015; 7: 3740–3747.
44. Le Rhun E, Taillibert S, Zairi F et al. Prolonged survival of patients with breast cancer-related leptomeningeal metastases. Anticancer Res 2013; 33: 2057–2063.
45. Boogerd W, van der Sande JJ, Moffie D. Acute fever and delayed leucoencephalophathy following low dose intraventricular methotrexate. J Neurol Neurosurg Psych 1988; 51: 1277–1283.
46. Kwon J, Chie EK, Kim K et al. Impact of multimodality approach for patients with leptomeningeal metastases from solid tumors. JKMS 2014; 29: 1094–1101.
47. Zagouri F, Sergentanis TN, Bartsch R et al. Intrathecal administration of trastuzumab for the treatment of meningeal carcinomatosis in HER2--positive metastatic breast cancer: a systematic review and pooled analysis. Breast Cancer Res Treat 2013; 139: 13–22.
48. Boogerd W, Dorresteijn LDA, van der Sande JJ, de Gast GC, Bruning PF. Response of leptomeningeal metastases from breast cancer to hormonal therapy. Neurology 2000; 55: 117–119.