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MINI-REVIEW

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SYSTEMIC CHEMOTHERAPEUTIC TREATMENT OF PATIENTS WITH BREAST CANCER BRAIN METASTASES

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Brain metastases of solid tumors are the most common intracranial neoplasms in adults. We provide a short overview of the role of the blood-brain barrier in the pathogenesis of breast cancer brain metastases, and the effectiveness of systemic anticancer therapy in the treatment of such patients.

***Key Words*: brain metastases, breast cancer, prognostic factors, effectiveness of systemic anticancer therapy, blood-brain barrier.**

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Brain tumors account for 85–90% of all tumors of the central nervous system (CNS). Brain metastases (BM) are 10 times more common than primary CNS tumors and diagnosed in 10–20% of all cancer patients. The incidence rate of BM in patients with solid tumors is steadily increasing, which can be explained by a number of factors. Firstly, this may be due to an improvement of diagnostic accuracy for brain tumors and increased alertness in maintaining the patients with tumors with a high risk of BM. Furthermore, an improvement in cancer treatment leads to the increased overall survival of patients with the ensuing risk of BM development for the rest of the life.

All malignant tumors are capable of producing BM in a varying degree. About 75% of all cases of BM occur in patients with lung cancer (40–50%), breast cancer (BC) (15–25%) and melanoma (5–20%) [1]. BM risk depends on the molecular subtype of BC. BM is detected in 50% patients with triple negative BC (TNBC) and in 30% of cases with HER2 overexpression [2]. In this article, we provide an overview of the role of the blood-brain barrier (BBB) in the pathogenesis of BC brain metastases (BCBM), and the effectiveness of systemic anticancer therapy (SAT) in treatment of patients with BCBM.

The presence of BM significantly worsens BC prognosis and decreases the median overall survival (OS) of patients depending on a number of factors that need to be considered for determining treatment options [1]. The prognostic importance of the clinical factors, morphological and molecular type of the primary tumor, Modified Breast Graded Prognostic Assessment (mB-GPA) for patients with BCBM has been developed with scores accounting for the age of patients, the number of metastases and the molecular subtypes of BC [3]. The median OS rates of patients with BCBM correlate well with the total scores gained by mB-GPA scale [3].

The prognosis determination is of importance for decision making in BCBM treatment. In patients with a poor prognosis, the appropriateness of anticancer therapy is debatable, and in patients with a good prognosis, multimodal palliative care can increase survival rates [4]. Moreover, disease prognostic scales can be used for improving the applicability, objectivity and validity of the results of clinical trials studying the treatment efficacy of BCBM.

ROLE OF BBB IN BCBM FORMATION

BBB is a physiological barrier to the penetration of toxic substances (including antitumor agents) and cancer cells into brain tissue. The most important BBB components are brain microvascular endothelial cells, astrocytes and microglial cells. Endothelial cells serve as a mechanical barrier, and astrocytes and microglia are able to destroy tumor cells. Upon overcoming BBB, the metastatic cells are protected from the immune system and the effects of most drugs, and cerebral endothelial cells, astrocytes and microglia are capable of producing cytokines and chemokines which are necessary to stimulate angiogenesis, tumor cells invasion, growth and proliferation [5].

The main factor determining drug resistance of BM is the availability of efflux transporters in BBB, which carry out the reverse transport and prevent drugs penetration into the brain tissue. These include P-glycoprotein (P-gp, gp170), multidrug resistance-associated proteins (MRP), breast cancer-resistance protein (BCRP, ABCG2) [6, 7]. Table 1 summarizes the main efflux transporters that prevent the drug penetration into the brain, and their substrates and inhibitors.

In patients with brain metastatic tumors, BBB has certain peculiar features. In contrast to the normal vascular network, the brain with BM is characterized by an increase in perivascular space, number and activity of pinocytotic vacuoles in endothelial cells characteristic of tumor vessels. Therefore, BBB in metastatic

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Abbreviations used: BBB – blood-brain barrier; BC – breast cancer; BCRP – breast cancer-resistance protein; BCBM – breast cancer brain metastases; BM – brain metastases; CNS – central nervous system; CR – complete response; mB-GPA – Modified Breast Graded Prognostic Assessment; MRP – multidrug resistance-associated proteins; ORR – objective response rate; OS – overall survival; PFS – progression-free survival; PR – partial response; SAT – systemic anticancer therapy; T-DM1 – trastuzumab emtansine; TNBC – triple negative breast cancer; WBRT – whole-brain radiotherapy.

Table 1. Substrates and inhibitors of the main BBB efflux transporters

Efflux transporters	Substrates	Inhibitors
P-gp	Doxorubicin, daunorubicin, docetaxel, paclitaxel, epirubicin, idarubicin, mitoxantrone, vinblastine, vincristine, etoposide, temozolomide, procarbazine, carmustin, topotecan, irinotecan, teniposide, carboplatin, erlotinib, dasatinib, sunitinib, sorafenib, imatinib mesylate, gefitinib, methotrexate, veliparib	Verapamil, cyclosporin A, reserpine, quinidine, dexverapamil, dexniguldipine, yohimbine, tamoxifen, toremifen, laniquidar, mitotane, biricodar valspodar, elacridar, biricodar, zosuquidar, tariquidar
MRP1	Etoposide, teniposide, daunorubicin, doxorubicin, epirubicin, melphalan, vinblastine, vincristine	Probenecid, sulfinpyrazone, verapamil, cyclosporin A, valspodar
MRP2		Probenecid, MK-571, leukotriene C4
MRP3		sulfinpyrazone, indomethacin, probenecid
MRP4	Methotrexate, 6-mercaptopurine, thioguanine	Probenecid
MRP5	6-mercaptopurine, thioguanine	Probenecid, sildenafil
MRP6	Actinomycin D, cisplatin, daunorubicin, doxorubicin, etoposide	Probenecid, indomethacin
BCRP	Mitoxantrone, methotrexate, topotecan, doxorubicin, 9-aminocamptothecin, temozolomide, imatinib, erlotinib, gefitinib, dasatinib, sunitinib, sorafenib, nilotinib veliparib, lomeguatrib	Elacridar, fumitremorgin C

tumors is more permeable than in the normal CNS and it is a capillary barrier rather than a full-scale BBB [8].

For being able to permeate to CNS, the substances must possess the following physicochemical properties: lipophilicity, molecular weight generally < 400–500 Da, and low hydrogen bonding ability. Most cytotoxic drugs do not meet the above physicochemical properties, which determine their limited penetration into brain, and this was a background for the design of methods to increase drug delivery to BM [9]. There are several ways to improve the delivery of substances into the CNS, e.g., osmotic shock, chemical conveyors, increasing dose and frequency of drug administration, implants made of biodegradable materials and others methods. Nevertheless, most of these methods required technically demanding manipulation with accompanying severe side effects and complications that prevented their application in daily clinical practice [10].

The methods based on the use of nanoparticles and efflux transporters inhibitors are particularly useful in routine clinical practice. The use of nanoparticles for delivery of anticancer drugs into brain has several advantages: overcoming drug resistance, increased bioavailability and specificity of the drug, a dose reduction without losing therapeutic effect and decreased side effects. The results of the clinical trials investigating the efficiency of nanoparticle-based anticancer treatment represent the basis for use of nanomedicines as the standard therapy of BC and other malignant tumors. Table 2 summarizes the nanoparticle-based anticancer drugs that could be useful in treating patients with BCBM [9, 11].

The effectiveness of nanoparticles and inhibitors of efflux transporters in patients with BM obtained through clinical trials are encouraging but subsequent studies of biodistribution, pharmacokinetics, toxicity, and side effects of therapy are required before inclusion of these drugs to standard protocol for CNS tumor treatment.

SYSTEMIC ANTICANCER THERAPY OF BCBM

Clinical evidence of SAT effectiveness for treatment patients with BCBM is contradictory. Main evidences of SAT effectiveness for BCBM treatment were obtained in patients with extracranial metastases, but the extracranial spread is known as more frequent cause of death than intracranial progression. [4]. The studies investigating the SAT efficacy in patients with BCBM demonstrate the response rate ranged from 4% to 38% and in some cases above 65% [12]. There is limited evidence of the SAT effectiveness in randomized trials, which prevents the development of the strategies for improving clinical effectiveness of SAT in BM patients without extracranial metastases and/or BM progression after local therapy. Table 3 presents the results of efficacy SAT in BCBM patients.

In a prospective study, the efficacy of the combination of cisplatin 100 mg/m^2 (on day 1) and etoposide 100 mg/m^2 (on days 1, 3 and 5 or on days 4, 6 and 8) IV every 3 weeks for a maximum of six cycles for treatment 56 patients with BCBM was analyzed [13]. 7 of 56 patients achieved complete response (CR), 14 achieved partial response (PR), 12 had no change, 15 had progressive disease, and 8 had insufficient treatment or response was not assessed. The objective response rate (CR + PR) was recorded in 21 (38%) patients with BCBM and median OS was 31 weeks.

Addeo R. *et al.* [14] studied the efficacy of the protracted low dose of oral vinorelbine and temozolomide after radiation therapy in 36 patients with BCBM. Temozolomide was administered orally at a daily dose of 75 mg/m^2 during whole-brain radiotherapy (WBRT). After 4 weeks off-therapy, patients received vinorelbine at 70 mg/m^2 orally on day 1, 3 and 5 for 3 consecutive weeks plus temozolomide at 75 mg/m^2 on days 1–21 every 4 weeks for 12 cycles. Objective response rate (ORR) was recorded in 19 (52%) from 36 patients (3 achieved CR and 16 — PR). The median of progression-free survival (PFS) and OS was 8 and 11 months, respectively.

In the phase III of the BEACON (BrEAst Cancer Outcomes with NKTR-102) trial, BM were reported in 67 of 852 patients with advanced BC. The efficacy of etirinotecan pegol (145 mg/m^2 IV once every 21 days) monotherapy was evaluated in 32 patients with

Table 2. Nanomedicines for BCBM treatment

Description	Indication
Albumin-bound paclitaxel nanospheres	BC, pancreatic cancer, NSCLC
Paclitaxel-loaded polymeric micelle	BC, NSCLC, ovarian cancer
Liposomal cisplatin encapsulated into liposome nanoparticles	BC, NSCLC
Liposomal doxorubicin	BC

Table 3. SAT efficacy in BCBM patients

SAT regiment	Number of patients	OR rate	OS median
Cisplatin + etoposide [13]	56	21 (38%)	31 weeks (0–287),
Temozolomide + vinorelbine [14]	36	19 (52%)	11 months
Etirinotecan pegol [15]	32	5 (15.6%)	All types – 10 months (7.8–15.7), HER2+ type – 16.1, Luminal A и B – 12.2 months, TNBC – 7.6 months
Temozolomide [16]	51	2 (4%),	No data
Gemcitabine + cisplatin [17, 18]	30 18	16 (53.3%) All types – 6 (33.4%); TNBC – 66.6%, Luminal A and B – 25%, HER2+ type – 12.5%	10 month median of PFS: All types – 5.6 months (2.4–8.8), TNBC – 7.4 months (2.4–12.3), Luminal A and B – 3.6 months, HER2+ type – 5 months
Carmustine + methotrexate [19]	48	11 (23%)	All types – 6,9 months (4.2–10.7), With HER2 overexpression (n = 8) – 14.1 months, Without HER2 overexpression – 5.9 months (3.9-8.2)
Capecitabine + lapatinib* [20]	799	29.2% (18.5–42.7)	11.2 months (8.9–14.1)
Trastuzumab [21]	56	No data	10.5 months (8.3–17.7)
Lapatinib [21]	30	No data	21.4 months (12.5–27.1)
Trastuzumab + lapatinib [21]	28	No data	25.9 months (18.5–30.1)
Neratinib + capecitabine [22]	37	18 (49%)	12-months OS is 63% (95% CI 43%–77%)
Trastuzumab emtansine [23]	53	13 (24.5%)	14 months (95% CI: 12.2–15.8)

Note: *BC with HER2 overexpression.

BCBM. In this trial, no CR was reported, partial regression was detected only in 5 (15.6%) and progressive disease revealed in 14 (43.8%) patients. The median of PFS was 3.1 months (range 1.8–4.0), and the median of OS was 10 months (range 7.8–15.7). The effectiveness of etirinotecan pegol in patients with BM depended on the BC molecular subtype. The median of OS was 16.1 months in patients with HER2+ type, 12.2 months with luminal types, and 7.6 months with TNBC. The results of BEACON trial show that the etirinotecan pegol is more effective for treatment of BM in patients with HER2+ and luminal types of BC [15].

In a study published by Siena *et al*. [16], the effectiveness of oral administration of temozolomide 150 mg/m^2 per day (1–7 days and 15–21 days every 28 days or 35 days) in 51 patients with BCBM was investigated. The ORR was revealed only in 4% (2) patients, the median OS was not evaluated and the median of PFS was 58 days. The results of this study indicate the low effectiveness of dose dense temozolomide monotherapy regimen in patients with BCBM.

Two studies evaluated the efficacy of the treatment of patients with BCBM to used cisplatin and gemcitabine regimen. Naskhletashvili *et al*. [17] reported about 30 patients with BCBM who received cisplatin 50 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1 and 8 IV every 3–4 weeks. The ORR registered in 53.3% (16) patients, and the median of OS was 10 months. Similar results were obtained by Erten *et al*. [18] in 18 patients with BCBM who were assigned to cisplatin 30 mg/m^2 plus gemcitabine 1000 mg/m^2 (on days 1 and 8) IV once every 21 days. The ORR depended of the BC molecular subtype and amounted to 33.4% for all BC types, 66.6% for TNBC, 25% in patients with luminal types and 12.5% among patients with HER2+ type. The OS of patients included in this study is not available. The median PFS also depended of the BC type and was the highest in patients with TNBC -7.4 months (range 2.4–12.3), 5 months in patients with HER2+ type, 3.6 months for luminal types and 5.6 months (range 2.6–8.8) for all BC types.

Jacot *et al*. [19] investigated the efficacy of carmustine (BCNU) 100 mg/m^2 (on day 1) and methotrexate 600 mg/m^2 (on days 1 and 15) IV every 28 days. Patients with HER2 overexpression were administered with trastuzumab 4 mg/kg (1 and 15 days) IV concurrently with each cycle of chemotherapy. In 11 (23%) patients CR or PR was detected. The median of PFS was 4.2 months (range 2.8–5.3), and the median of OS was 6.9 months (range 4.2–10.7) in patients with all molecular BC subtypes. Median of OS was higher in patients with HER2 overexpression, and was 14.1 months *vs* 5.9 months among patients with HER2-negative BC.

The efficacy of concurrent use of capecitabine and lapatinib for treatment of BCBM with HER2 overexpression has been studied in several trials. A meta-analysis of 12 trials for a total of 799 patients with HER2/neu-positive BCBM revealed that ORR was 21.4% (11.7–35.9). After excluding patients who received lapatinib monotherapy, the ORS rate was 29.2% (18.5–42.7). The median of OS was 11.2 months (range 8.9–14.1) and PFS was 4.1 months (range 3.1–6.7) [20].

In a retrospective multicenter study, Yap *et al*. [21] evaluated the efficacy of anti-HER2 therapy in patients with HER2-positive BCBM. Data analysis included 280 BM patients with HER2-positive BC. 260 (92.9%) patients previously received radiotherapy, 160 (57.1%) — chemotherapy and 114 (40.7%) — anti-HER2 therapy. Among 114 patients, who received anti-HER2 therapy, 56 (49.1%) patients received trastuzumab alone, 30 (26.3%) lapatinib alone and 28 (24.6%) trastuzumab in combination with lapatinib. The median OS was significantly improved in patients who received combination anti-HER2 therapy and

amounted to 10.5 months (range 8.3–17.7) in the trastuzumab group, 21.4 months (range 12.5–27.1) in the lapatinib group and 25.9 months (range 18.5–30.1) in the trastuzumab + lapatinib group.

The multicenter phase II study "TBCRC (Translational Breast Cancer Research Consortium) 022" has investigated the efficacy of capecitabine 750 mg/m^2 twice a day for 14 days plus neratinib 240 mg orally once a day. Among 37 patients with BM of HER2-positive BC, 65% had previous WBRT. ORR was reported in 18 (49%) patients and the 12-month OS rate was 63% (95% CI 43% -77%) [22].

Fabi *et al*. [23] investigated the clinical efficacy of trastuzumab emtansine (T-DM1) in 87 adult women with HER2-positive BCBM. Response to treatment T-DM1 was available from 53 of the selected 87 patients (60.9%). ORR was recorded in 13 (24.5%) patients: 2 (3.8%) patients demonstrated CR, 11 (20.7%) — PR, and 16 (30.1%) patients — no response. The median PFS was 7 months (range 5.4–8.6) and the median of overall survival was 14 months (range 12.2–15.8). The median follow-up was 16 months (range 1–55).

In recent years, significant progress has been reached in diagnosis, prognosis and treatment of patients with BCBM. The development of prognosis scales for assessing OS is a premise for determining an appropriate individualized treatment of patients with BM in routine clinical practice and also allows achieving the validity and applicability of the clinical trials results. However, a major drawback of the existing prognostic scales is that they do not consider mortality from extracranial progression.

For a long time, surgical treatment and radiotherapy were the standard of care for most patients with BCBM, and SAT was mainly used in patients with extracranial metastases. Nevertheless, the local therapy is not effective and OS remains low in patients with BCBM, especially in patients with extracranial metastases. The low efficacy of standard SAT for BCBM is associated with the peculiarities of BBB. Numerous efflux transporters prevent the penetration of most drugs used for the treatment of BCBM. Promising methods to overcome BBB include the modification of the physicochemical properties of existing drugs, development of new drugs, and the use of efflux transporters inhibitors. The results of the studies of the clinical effects of nanoparticles of anticancer drugs and efflux transporters inhibitors in patients with BCBM are encouraging, but further studies are needed to investigate biodistribution, pharmacokinetics, toxicity, and side effects of the therapy. Further studies should investigate the mechanisms of the development of CNS metastases and factors predicting their high risk. The multidisciplinary approach to the treatment of patients using prognostic scales will lead to a more effective combined therapy to maintain neurological and neurocognitive function for achievement of the best quality of life of the BCBM patients.

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СИСТЕМНЕ ХІМІОТЕРАПЕВТИЧНЕ ЛІКУВАННЯ ХВОРИХ З МЕТАСТАЗАМИ РАКУ ГРУДНОЇ ЗАЛОЗИ У ГОЛОВНИЙ МОЗОК

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Метастази солідних пухлин у головний мозок є найбільш поширеними внутрішньочерепними неоплазмами у дорослих. Наведено стислий огляд ролі гематоенцефалічного бар'єру в патогенезі метастазів раку грудної залози у головний мозок та ефективності системної протиракової терапії у лікуванні цієї категорії хворих.

Ключові слова: метастази у головний мозок, рак грудної залози, прогностичні фактори, ефективність системної протиракової терапії, гематоенцефалічний бар'єр.