Chapter 3

Management of Brain Metastases from Solid Tumors

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Abstract

Brain metastases (BM) are most common intracranial tumors in adults. Recently, significant progress has been shown in diagnosing, prognosis, and treating patients with BM of various malignant tumors. The treatment decisions must be based on the disease prognosis and include radiation therapy, surgery, systemic antitumor therapy, or a combination thereof. Systemic therapy capable of preventing BM or which affects both intracranial and extracranial disease is of paramount importance in the treatment of BM patients. The purpose of this chapter is to consider important prognostic factors that can determine treatment decisions, review the role of blood–brain barrier (BBB), and systemic anticancer treatment to manage BM from solid tumors.

Keywords: brain metastases, solid tumors, prognostic scores, blood–brain barrier, systemic anticancer treatment

1. Introduction

Brain tumors constitute for 85–90% of all tumors of the central nervous system (CNS) [1]. Brain metastases (BM) are ten times more prevalent than primary tumors of the central nervous system (CNS) and are diagnosed in 10–20% of all cancer patients. The frequency of detection of BM is steadily increasing, which can be explained by such causes. First, this may be due to the increased availability and improvement of diagnostic methods for brain tumors. Second, the use of screening brain examinations of patients with tumors has a high incidence of the CNS metastases. Third, the improved effectiveness of anticancer treatment leads to increased overall survival rates of patients and increased risk of developing BM [2]. All malignant tumors have the potential to provide distant metastasis to the brain. Approximately 75% of all cases of brain metastases are due to patients with lung cancer (40–50%), breast cancer (15–25%),

and melanoma (5–20%) [1]. Among the remaining 25%, BM is more predominant in patients with renal cell cancer (4–17%) and gastrointestinal cancer (0.6–3%) [3, 4]. At autopsy, BM are found to be 1.5–3 times more frequent and are detected in more than 65% of patients with lung cancer, 30–40% of patients with malignant melanoma (MM), and 30% of patients with breast cancer (BC). About 85% of metastatic lesions are located in the brain hemispheres, 15% in the cerebellum, and 5% in the brain stem [5].

The aim of this review is to consider important prognostic factors that can determine the treatment decisions and to review the role of blood–brain barrier (BBB) and systemic anticancer treatment (SAT) to manage BM from solid tumors.

2. Determination of prognosis of patients with brain metastases

The BM patients have significantly worsened the prognosis because the median overall survival (OS) in BM cases varies from 2.79 to 25.3 months. The disease prognosis depends on a number of factors that must be taken into account when determining the treatment algorithm of patients with BM. **Table 1** presents prognostic scales assessment of the prognosis in patients with cerebral metastases [6].

Table 1 presents the assessment scales of the overall survival prognosis of brain metastases patients have a number of limitations who restrict their use in routine clinical practice and clinical trials. The Recursive partitioning analysis (RPA) scale can be used only if the patient is shown to be carrying out the whole brain radiotherapy (WBRT). RPA cannot be used on patients who underwent palliative surgery, stereotactic radiosurgery (SRS), and/or systemic anticancer therapy, but this treatment option has significant effect on BM patient's survival. Another limiting factor of the RPA score system is that it does not take into account the size and number of BM. The drawbacks of the Rotterdam score system are the lack of consideration of the patient's age, number, and size of BM. The most complete predictive system is the Score

Prognostic factors	RPA	Rotterdam score	SIR	BSBM	GPA	DS-GPA
Age	+	—	+	—	+	+
Performance status	KPS	ECOG	KPS	KPS	KPS	KPS
Extracranial metastases	+	+	+	+	+	+
Control of primary tumor	+	—	+	+	—	—
Number of BM	—	—	+	—	+	+
Volume of BM	—	—	+	—	—	—
Response to steroids	—	+	—	—	—	—
Number of classes	3	3	3	4	4	4

RPA: Recursive partitioning analysis; SIR: Score Index for Radiosurgery; BSBM: Basic Score for Brain Metastases; GPA: Graded Prognostic Assessment; DS-GPA: Disease specific Graded Prognostic Assessment; KPS: Karnofsky performance status; ECOG: Eastern Cooperative Oncology Group Score.

Table 1. Prognostic scores for brain metastasis patients.

Index for Radiosurgery (SIR) scale, but it has not been widely used in clinical practice since it does not take into account systemic influence to disease. The Basic Score for Brain Metastases (BSBM) scale is an analogue of RPA scale and takes into account the impact of SRS on the survival of BM patients, but it does not take into account the patient's age and the effectiveness of systemic drug therapy. In 2007, the Graded Prognostic Assessment (GPA) scoring system was proposed, which took into account four factors: age, Karnofsky performance status (KPS), availability of extracranial metastases, and the number of BM. A number of studies have proved the prognostic significance of these indicators, and the GPA scale is recognized as the most objective and most commonly used scoring system for survival prognosis of BM patients. However, GPA system does not consider the influence of primary tumor type for prognosis of BM, which has different sensitivity to the drug and radiation therapy. To account the influence of the prognostic value of the histological and molecular type of the primary tumor, a Disease Specific Graded Prognostic Assessment (DS-GPA) system was developed. **Table 2** presents the factors and prognosis of overall survival rates of patients with BM from lung cancer, MM, BC, renal cell (RCC), and gastrointestinal cancer (GI) [7].

Prognostic factor	**GPA scale score**					**Total score**	**Median of overall survival, months (95% CI)**	
	0	**0.5**	**1.0**	**—**	**—**			
Lung cancer								
Age (years)	>60	50–60	< 50	—	—		NSCLC	SCLC
KPS	<70	70–80	90–100	—	—	0–1	3.02 (2.63–3.84)	2.79 (1.83–3.12)
Extracranial metastases	Yes	n/a	No	—	—	1.5–2.0	5.49 (4.83–6.40)	4.90 (4.04–6.51)
				—	—	2.5–3.0	9.43 (8.38–10.80)	7.67 (6.27–9.13)
Number of BM	> 3	2–3	1	—	—	3.5–4.0	14.78 (11.80–18.80)	17.05 (4.70–27.43)
Malignant melanoma								
Prognostic factor	GPA scale score					Total score	Median of overall survival, months (95% CI)	
	0	1.0	2.0	—	—			
KPS	<70	70–80	90–100	—	—	0–1	3.38 (2.53–4.27)	
Number of BM	>3	2–3	1	—	—	1.5–2.0	4.7 (4.07–5.39)	
						2.5–3.0	8.77 (6.74–10.77)	
						3.5–4.0	13.23 (9.13–15.64)	
Breast cancer								
Prognostic factor	GPA scale score					Total score	Median of overall survival, months (95% CI)	
	0	0.5	1.0	1.5	2.0			
Age (years)	≥ 60	< 60	—	—	—	0–1	3.35 (3.13–3.78)	

Prognostic factor	**GPA scale score**					**Total score**	**Median of overall survival, months (95% CI)**
	0	**0.5**	**1.0**	**—**	**—**		
KPS	≤ 50	60	70–80	90–100	—	1.5–2.0	7.70 (5.62–8.74)
Molecular type	Triple negative	—	Lum A	HER2-type	Lum B	2.5–3.0	15.07 (12.94–15.87)
						3.5–4.0	25.30 (23.10–26.51)
Renal cell cancer							
Prognostic factor	GPA scale score					Total score	Median of overall survival, months (95% CI)
	0	1.0	2.0	—	—		
KPS	<70	70–80	90–100			0–1	3.27 (2.04–5.10)
Number of BM	>3	2–3	1			1.5–2.0	7.29 (3.73–10.91)
						2.5–3.0	11.27 (8.80–14.80)
						3.5–4.0	14.77 (9.73–19.79)
Gastrointestinal cancer							
Prognostic factor	GPA scale score					Total score	Median of overall survival, months (95% CI)
	0	1.0	2.0	3.0	4.0		
KPS	< 70	70	80	90	100	0–1	3.13 (2.37–4.57)
						1.5–2.0	4.40 (3.37–6.53)
						2.5–3.0	6.87 (4.86–11.63)
						3.5–4.0	13.54 (9.76–27.12)

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; KPS: Karnofsky performance status; n/a: not applicable; ER: estrogen receptors; PR: progesterone receptors; Her2/neu (ErbB2): human epidermal growth factor receptor 2; Triple negative: ER-negative, PR-negative, Her2/neu-negative; Lum A: ER-positive and/or PR-positive, Her2/neu-negative; HER2-type: ER-negative, PR-negative, Her2/neu-overexpression/amplification; Lum B: ER-positive and/or PR-positive, Her2/neu-overexpression/amplification.

Table 2. Median of overall patient survival with BM from solid tumors according to the DS-GPA scale prognosis indices.

Prognostic scores are very important to take decisions on the most appropriate treatment options for patients with BM in each case. The need for palliative treatment for patients with poor prognosis is controversial, but patients with good prognosis must receive multidisciplinary palliative therapy to increase overall survival rates [8]. Moreover, prognostic score systems can be used to increase the applicability, objectivity, and validity of the clinical trial results that investigate the effectiveness of treatment in patients with BM from various malignant tumors.

3. Role of the blood-brain barrier in the formation of brain metastases

The blood-brain barrier (BBB) plays a prominent role in the brain colonization by malignant tumor cells and determines the effectiveness of drug therapy. BBB is a natural obstacle for the

penetration of malignant tumor cells within the brain parenchyma. Endothelial cells of brain vessels serve as a mechanical barrier, and astrocytes and microglia are capable of destroying tumor cells. However, after brain colonization, the cerebral endothelial cells, astrocytes, and microglia provide crucial support in the growth and proliferation of tumor cells, and BBB protects cancer cells from influencing the immune system and most anticancer drugs [9].

The penetration of the BBB depends on its functional condition, as well as on the morphological, molecular, and genetic characteristics of tumor cells, that may explain the opportunity of some malignant cells to easily overcome this highly selective barrier relatively. For example, the compound density reduction of the cerebral endothelial cells, which increase the permeability of BBB, was detected in severe CNS diseases such as Alzheimer's disease, multiple sclerosis, and primary and metastatic brain tumors [10]. The expression CDH2 (N-cadherin), KIFC1, and FALZ genes in a primary tumor in lung cancer patients with BM determine the high cerebral metastatic potential of lung cancer cells. The CDH2 gene encoded N-cadherin (cadherin-2 or neural cadherin (NCAD)) is involved in tumor progression, such as migration and invasion of tumor cells, including in the CNS. Also, in non-small cell lung cancer, patients' expression of DCUN1D1 squamous cell carcinoma-associated oncogene may promote the tumor cell migration through the BBB and development of BM. High KLF6-SV1 expression in prostate cancer cells associated with poor patient's survival predict a high risk of lymph nodes, brain, and bones metastasis [11]. Several factors have been identified in breast cancer cells that promote the BC cell migration through the BBB, such as cyclooxygenase-2 (COX2), heparin-binding epidermal growth factor-like growth factor (HB-EGF), and ST6GALNAC5 ((alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide-alpha-2,6-sialyltransferase 5 ST6). The ST6GALNAC5 gene expression is recognized as a tumor cells BBB migration specific marker because COX2 and HB-EGF are associated with the brain and lung metastases. In vitro studies of melanoma cells were shown to increase the BBB permeability by reduce transendothelial electrical resistance of endothelial cells. Expression of melanotransferrin (MELTF, CD228, MAP97, MTF1, MTf, MFI2) and signal transducer and transcriptional activator 3 (STAT3) can serve as potential markers of cerebral metastases in patients with melanoma. The availability of MELTF on the melanoma cell membrane determines their ability to penetrate through the BBB. High levels of STAT3 in melanoma BM compared to primary tumor cells indicate a relationship between STAT3 expression and tumor cell migration to the brain [9]. Thus, the identification of tumor cells specific markers of penetration through the BBB can be a basis for the development of specific methods for the prevention of BM. The main factor of the BM treatment resistance is BBB efflux transporters which prevent the drug's penetration into the brain parenchyma. **Table 3** shows the main drug efflux transporters of the BBB and their substrates and inhibitors [12].

P-glycoprotein (Pgp, gp170) is a protein encoded by the gene MDR1 (multidrug resistance 1) whose main function is the active removal of many different substances, including some drugs, from the cell cytoplasm to the intercellular environment. Pgp molecules are found in the proximity of the apical membrane of the choroid plexus secretory cells and at the luminal membrane of the brain capillary, which allows transferring most of the Pgp substrates from the endothelium and parenchyma of the BM to the cerebrospinal fluid and blood. The role of Pgp in the maintenance of BBB was investigated through in vivo studies. Studies conducted on MDR1 gene knockout mice revealed an increased effect on brain parenchyma of parenterally administered P-glycoprotein substrates compared with wild-type mice. The use

Efflux transporter	Substrates	Inhibitors
P-glycoprotein	Doxorubicin, daunorubicin, docetaxel, paclitaxel, epirubicin, idarubicin, vinblastine, vincristine, etoposide	Verapamil, cyclosporine A, quinidine, valspodar, elacridar, biricodar, zosuquidar, tariquidar
MRP1	Etoposide, teniposide, daunorubicin, doxorubicin, epirubicin, melphalan, vincristine, vinblastine	Probenecid, sulfinpyrazone, MK-571, cyclosporin A, verapamil, 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, SN-38, topotecan, imatinib, erlotinib, gefitinib	Elacridar, fumitremorgin C

Table 3. Substrates and inhibitors of the main drug efflux transporters of the BBB.

of Pgp-inhibitors in wild-type animals was accompanied by an increase in the brain penetration of Pgp substrates including anticancer drugs (vincristine, paclitaxel, daunorubicin, etc.). Similar results were obtained on using P-glycoprotein inhibitors (verapamil and cyclosporin A) to increase the BBB penetration [7].

Multidrug resistance-associated proteins (MRP) are the ABCC family of transporter (ATP-binding cassette subfamily C) proteins, which are an important component determining the selective permeability of the BBB for different drugs [13]. In vivo studies performed on mice with knockout of the MRP1 gene were found to have higher accumulation of MRP1 substrates, including etoposide versus wild-type mice. And after the use of the inhibitor MRP1 (probenecid), a double increase in the concentration of fluorescein in the brain was observed [7].

Breast cancer-resistant protein (BCRP, ABCG2). ABCG2 (ATP-binding cassette subfamily G member 2) is an efflux transporter called the breast cancer resistance protein, since it was first detected in the drug-resistant MCF-7 human breast cancer cells [14]. BCRP is an important component in determining BBB permeability, and its concentration in the CNS endothelium is greater than the P-glycoprotein and MRP1 concentrations. In mice with BCRP1 gene knockout, the imatinib concentration in the brain parenchyma was increased 2.5-fold in knockout versus control mice. The administration of a BCRP inhibitor (elacridar) in wild-type mice results in an increase in the penetration of imatinib 4.2 times, while in knockout MDR1 gene mice, elacridar increases cerebral cells absorption of BCRP substrates such as prazosin and mitoxantrone [15].

The structure of BBB in brain metastatic tumors has some features. In contrast to the normal cerebral vascular network, the brain metastases have an increased perivascular space, number, and activity of pinocytotic vacuoles in endothelial cells; these features are more typical for tumor vessels than for the CNS vessels. Thus, metastatic tumor BBB is more permeable than in the normal CNS parenchyma and is more likely to be a capillary barrier than a performed BBB [7].

3.1. Influence of radiation therapy on the BBB permeability

Brain radiotherapy is the standard of palliative care as per the guidelines of clinical practice for patients with BM. In several in vivo studies in rats after brain radiation were such changes observed: dilation and thickening of the blood vessel wall, increase of endothelial cell nuclei, astrocyte hypertrophy, and 60% decrease the P- glycoprotein concentration [7]. These changes in the brain of rats were a prerequisite for a hypothesis about influence of radiation to the BBB permeability and increase in the clinical effectiveness of chemotherapy in patients with BM, because radiation could raise the penetration of anticancer drugs into the brain parenchyma. Murrell D.H., et al. (2016) did not found changes in BBB permeability at the 1st and 11th days after radiation in mice after WBRT therapeutically relevant doses to human equivalent doses. The results of clinical studies have not revealed an increase in clinical effectiveness in the concurrent use of radiation and chemotherapy [16]. The BBB permeability modification under the influence of radiation on the BM at the moment is controversial and needs further study.

3.2. Increasing of drug's penetrations through the BBB

The ideal compound to treat BM must have the following physicochemical properties such as low molecular weight, lipophilicity, and absence of ionization at physiological pH. Physicochemical properties of most anticancer drugs not match the above specifications, that limit BBB permeability of drugs, and was a basis for developing ways to deliver drugs to the brain. There are several ways to improve the delivery of substances to the central nervous system, for example, the BBB opening under conditions of temporary osmotic shock, the use of chemical vectors (transporters), increasing the dose and the frequency of drug administration, the use of implants from biodegradable materials, and so on. All methods of increasing drug delivery to the CNS can be attributed to one or more of the three main approaches: change in the chemical structure and/or physicochemical properties, and/or drug dose (concentration), increasing the BBB permeability, and using alternative routes of administration. The low efficiency of most approaches, with the need for performing technically complex manipulations that are accompanied by pronounced side effects and complications, limits their use in everyday clinical practice [17].

The most available methods for improving the drug delivery to BM in routine clinical practice are the use of nanoparticles and efflux transporters inhibitors (**Table 3**). Application of nanoparticles for targeted drug delivery has several advantages: overcoming chemoresistance, increasing the drug bioavailability and specificity, dose reduction without loss of efficacy, and reduction in adverse reactions. The clinical studies performed on the effectiveness of the nanoparticle application with anticancer drugs served as a basis for the use of these drugs as standard therapy for BM patients. **Table 4** shows chemotherapeutic drugs with nanoparticles, the use of which has been approved by the US Food and Drug Administration (FDA) for the treatment BM patients [18].

The clinical trial results of the efficacy of anticancer nanomedicines and efflux transporter inhibitors in BM patients are encouraging, but further trials are needed to study biodistribution, pharmacokinetics, toxicity, and side effects for inclusion of this drug practice guidelines for the management of CNS tumors.

Name	Description	Indication
DaunoXome	Liposomal daunorubicin	First-line therapy against advanced Kaposi's sarcoma associated with HIV
DepoCyt	Liposomal cytarabine	Lymphomatous meningitis
Oncaspar	L-asparaginase conjugated with monomethoxypolyethylene glycol (mPEG)	Acute lymphoblastic leukemia
Abraxane	Albumin-bound paclitaxel nanospheres	Pancreatic cancer, NSCLC, breast cancer
Myocet	Liposomal doxorubicin	Breast cancer
Marqibo	Liposomal vincristine	Acute lymphoblastic leukemia
Genexol	Paclitaxel-loaded polymeric micelle	Breast cancer, NSCLC, ovarian cancer
Onivyde	Liposomal irinotecan	Pancreatic cancer

Table 4. Anticancer nanomedicines approved by the FDA.

4. Decision-making of palliative care options of BM patients

The decision-making of BM patient's treatment must rely on some factors such as: the patient Karnofsky performance status; the number, size, and location of BM; the primary tumor type; and the presence and control of extracranial metastases. **Table 5** presents palliative treatment options of BM patients depending on the set of predictive factors listed above [7].

Type of palliative treatment	Indications
Systemic anticancer therapy	- BM from systemic anticancer therapy-sensitive primary tumor;
	- Asymptomatic BM, detected during planning of systemic anticancer therapy;
	- BM from PT with identified molecular alteration amenable to targeted therapy;
	- Poor effect of other treatment options in case presence of potentially effective systemic anticancer agents.
Whole brain radiotherapy	- Multiple MGM (> 3–10), especially if the primary tumor is sensitive to radiation therapy;
	- Large (4 cm) BM;
	- After surgical resection of a dominant large metastatic tumor and the presence of multiple BM (> 3–10);
	- BM disease progression during systemic drug therapy;
	- Salvage therapy for recurrent BM after SRS or WBRT failure.
SRS	- Oligo-BM or multi-BM (≤3), especially if primary tumor is known to be radiotherapy resistant;
	- After surgical resection of a single BM if it diameter > 3 cm and/or BM localized in the posterior cranial fossa;
	- Local recurrence after surgical resection of a single BM;
	- Salvage therapy for recurrent oligo-BM or multi-BM (≤ 3) after WBRT failure.

Type of palliative treatment	Indications
Surgical resection	- BM localized (or most of it) in the brain critical structures (eyes, optical tracts, brainstem, etc.);
	- Oligo-BM (1–2), especially when associated with extensive brain swelling;
	- If morphological examination of CNS lesions is necessary.
Supportive care alone	- Systemic disease progression after several types of palliative therapy in patients with poor performance status.

SACT: systemic anticancer therapy, WBRT: whole brain radiotherapy, SRS: stereotactic radiosurgery.

Table 5. Decision-making of palliative treatment options of BM patients.

According to **Table 5**, patients with brain metastases are not receiving anticancer therapy only if they have progression of the disease after receiving several types of anticancer therapy and them performance status stay poor after adequate supportive care [19].

5. Systemic anticancer therapy for BM patients

The evidence of the effectiveness of systemic anticancer therapy in patients with BM is contradictory. Nevertheless, SACT may be an effective treatment option for patients with BM, because it prolongs overall survival, especially in patients with metastatic lesions in other organs, since the progression of extracranial metastases is a common cause of death of most patients [20]. The BBB is a natural barrier for most anticancer drugs, and it is the primary mechanism responsible for BM resistance to systemic therapy. Several retrospective clinical studies determined that the chemotherapy was effective in 4–38% of patients with BM having various solid tumors [21]. Results are found to be limited on randomized trials on the effectiveness of anticancer drugs, which hinder the development of a generally accepted strategy for effective SACT of BM, especially in patients without extracranial metastases and/or progression after BM local therapy (surgery, radiotherapy). **Table 6** presents the effectiveness of chemotherapy in patients with brain metastases from NSCLC, melanoma, and breast cancer.

In a study performed by Franciosi et al. (1999), 107 patients with BM received a combination of cisplatin 100 mg/m^2 (IV day 1) + etoposide 100 mg/m^2 (IV on days 1, 3, and 5 or on days 4, 6, and 8) every 21 days, was continued to a maximum of 6 cycles. The distribution according to the primary tumor site was non-small cell lung cancer in 43 (40%) patients, breast cancer in 56 patients (52%), and malignant melanoma in 8 (8%). Among the 107 patients with BM, 7 BC patients achieved complete response (CR) (13%), 3 NSCLC patients achieved CR (7%), and none of the 8 MM patients achieved an objective response. The objective response rate (ORR) of the chemotherapy (CR + partial response (PR)) was recorded in 37.5% of patients with BC and in 30% of patients with NSCLC. The median survival was 7.5 months (range 0–91.5+ months) for patients with NSCLC, 7.2 months (range 0–67 months) for patients with BC, and 4.0 months (range 0.5–11.2 months) for patients with MM. This chemotherapy regime is effective for patients with BM from BC and NSCLC [22].

Chemotherapy regimen	Primary tumor type	Number of patients	Response rate	Median overall survival (months)
Cisplatin + etoposide	NSCLC, breast cancer, melanoma	Total 107 (100%): NSCLC–43(40%), BC–56 (52%), MM–8 (8%)	Total 34 (32%): NSCLC–13 (30%), BC–21 (37.5%), MM–0	NSCLC–7.5 (0–91,5+), BC–7.2 (0–67), MM–4.0 (0,5–11.2)
Etirinotecan pegol	BC	32	5 (15.6%)	All molecular types - 10 (7,8–15.7); Triple negative – 7,6; Lum A and B–12.2; HER2-type–16.1.
Temozolomide	NSCLC, breast cancer, melanoma	Total 157 (100%): NSCLC–53(34%), BC–51 (32%), MM–53 (34%)	Total 10 (6%): NSCLC–3 (6%), BC–2 (4%), MM–5 (9%)	NSCLC–5.7; BC–n/a, MM–3.3.
Gemcitabine + carboplatin	NSCLC	66	56 (29%)	7.6 (6.3–10.1)
Gemcitabine + paclitaxel		64		8.2 (4.6–10.5)
Carboplatin + paclitaxel		64		7.7 (6.1–10.2)
Cisplatin + gemcitabine	BC	30	16 (53.3%)	10
		18	All molecular types: 6 (33.4%); Triple negative: 66.6%, Lum A and B: 25%, HER2-type: 12.5%	Median PFS: All molecular types – 5.6 (2.4–8.8); Triple negative – 7.4 (2.4–12.3); Luml A and B: –3.6; HER2-type: 5.
Carmustine + methotrexate	BC	48	11 (23%)	All molecular types: 6.9 (4.2–10.7); Her2/neu: overexpression/amplification (n = 8): 14,1; Her2/neu-negative: 5.9 (3,9–8.2).
Pemetrexed	NSCLC	39	15 (38.4%)	10

Chemotherapy regimen	Primary tumor type	Number of patients	Response rate	Median overall survival (months)
Pemetrexed + cisplatin	NSCLC	43	18 (41.9%)	7.4 (5.8–9.6)
Capecitabine + lapatinib	BC with Her2/neu: overexpression/ amplification	799	29.2% (18.5–42.7)	11.2 (8.9–14.1)

NSCLC: non-small cell lung cancer, BC: breast cancer, MM: malignant melanoma, Triple negative: ER-negative, PR-negative, Her2/neu-negative; Lum A: ER-positive and/or PR-positive, Her2/neu-negative; HER2-type: ER-negative, PR-negative, Her2/neu-overexpression/amplification; Lum B: ER-positive and/or PR-positive, Her2/neu-overexpression/amplification, n/a: not applicable.

Table 6. The efficacy of systemic chemotherapy in patients with brain metastases.

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In open-label, multicentre, randomised phase 3 study (BEACON; BrEAst Cancer Outcomes with NKTR-102), was study the effectiveness of etirinotecan pegol 145 mg/m² (IV day 1 every 3 weeks) monotherapy in 32 BC patients with BM previously treated with an anthracyclines, a taxanes, and capecitabine. In this study, there were no recorded cases of CR, partial response was detected only in 5 (15.6%), and 14 (43.8%) patients had disease progression. With a median follow-up of 21.1 months, the progression-free survival (PFS) for 32 patients was 3.1 months (range 1.8–4.0 months), and the median OS 10 months (range 7.8–15.7 months). The efficacy of etirinotecan pegol in BM patients depended on the BC molecular type and median OS was: 16.1 months in HER2-type, 12.2 months in luminal A and B types, and 7.6 months in patients with triple negative BC. The results of the BEACON study recommend the etirinotecan pegol for treatment in BM patients with HER2-type and luminal breast cancer types [23].

Siena and co-workers (2010) reported on a nonrandomized multicenter phase II study of 157 patients with cerebral metastases of NSCLC 53 (34%), BC 51 (32%), and melanoma 53 (34%) who received temozolomide 150 mg/m² per day (oral administration for 1–7 and 15–21 days every 28 or 35 days). The BM complete response was recorded in one (<1%) patient with NSCLC. Among 157 patients, 9 (6%) had PR, and stabilization of disease (SD) was detected in 31 (20%) of 157 patients. The PFS was 66, 58, and 56 days for NSCLC, breast cancer, and melanoma BM patients, respectively. The median OS for patients with NSCLC was 172 days, melanoma was 100 days, and was not applicable in the breast cancer group. The results of this study indicate a low effectiveness of high dose-dense temozolomide regimen for the treatment of brain metastases from NSCLC, BC, and melanoma [24].

At randomized phase 3 clinical trial comparing 3 chemotherapy regimens in 194 patients with clinically stable BM from NSCLC, all patients were randomized into 3 groups: group 1 ($n = 66$) received the gemcitabine 1000 mg/m² (on days 1 and 8) + carboplatin AUC 5.5 (on day 1), group 2 ($n = 64$) received gemcitabine 1000 mg/m² (on days 1 and 8) + paclitaxel 200 mg/m² (on day 1), and group 3 ($n = 64$) received carboplatin AUC 5.5 (on day 1) + paclitaxel 225 mg/m² (on day 1) IV every 3 weeks, was continued to a maximum of 6 cycles. The study results showed the same clinical efficacy for all three regimens. Median OS was 7.6 months (range 6.3–10.1 months) for patients from group 1, 8.2 months (range 4.6–10.5 months) for group 2, and 7.7 months (range 6.1–10.2 months) for group 3 [25].

Two studies evaluated the efficacy of BM patients from BC treatment with cisplatin + gemcitabine chemotherapy regimen. Naskhletashvili and colleagues reported results of treatment in 30 patients with BC brain metastases who received cisplatin 50 mg/m² (on days 1 and 8) + gemcitabine 1000 mg/m² (on days 1 and 8) IV every 3–4 weeks. ORR for chemotherapy was recorded in 6 (53.3%) patients, and the median OS was 10 months [26]. Similar results were obtained by Erten et al. [27]. In this study, 18 BC patients with BM who were treated with cisplatin 30 mg/m² (on days 1 and 8) + gemcitabine 1000 mg/m² (on days 1 and 8) IV every 21 days. The ORR depended on the primary tumor molecular type and was 33.4% for all BC molecular types, 66.6% for triple-negative BC, 25% for luminal types, and 12.5% for patients with HER2- type. The overall survival rates of these study patients have not been reported. Median PFS also depended on the type of breast cancer and was greatest in patients with triple-negative breast cancer at 7.4 months (range 2.4–12.3 months); in patients with HER2-type at 5 months, with luminal types at 3.6 and 5.6 months (range 2.6–8.8 months) for all breast cancer molecular types [27].

Jacot and co-workers reported on 48 breast cancer patients treated with carmustine 100 mg/m^2 (on day 1) + methotrexate 600 mg/m^2 (on days 1 and 15) IV of a 28-day cycle. Patients with Her2/neu overexpression and/or amplification received trastuzumab 4 mg/kg (on days 1 and 15) IV during each cycle of chemotherapy. The ORR was detected in 11 (23%) patients. The PFS was 4.2 months (range 2.8–5.3 months), and the median OS at 6.9 months (range 4.2–10.7 months) for all BC molecular type. The median OS was different in patients with the Her2/neu overexpression and/or amplification tumors (14.1 months) and without Her2/neu overexpression and/or amplification BC (5.9 months) [28].

The efficacy of pemetrexed in NSCLC patients with BM was evaluated in several studies. Bearz et al. (2009) reported about clinically significant efficacy monotherapy of pemetrexed 500 mg/m^2 IV (on day 1) every 3 weeks as a 2- or 3-line chemotherapy. ORR was detected in 15 (38.4%) from 39 patients with BM from NSCLC, and median OS was 10 months. Barlesi et al. (2011) evaluated the efficacy of the regimen pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 (IV on day 1) every 3 weeks for 6 cycles. The ORR was recorded in 18 (41.9%) of 43 patients with BM from NSCLC, and the median OS was 7.4 months (range 5.8–9.6 months). The concurrent administration of WBRT with chemotherapy pemetrexed + cisplatin significantly increases the treatment effectiveness according to the results obtained by Dinglin et al. (2013). The ORR of the pemetrexed + cisplatin + WBRT regimen was detected in 28 (68.3%) of 41 NSCLC patients with BM, and median OS was 12.6 months [29].

The efficacy of combination capecitabine and lapatinib for the treatment of Her2/neu overexpression on BC patients with BM has been investigated in several studies. A systematic review and meta-analysis of 12 studies, for total 799 patients with BM from Her2/neu-positive breast cancer, was show revealed ORR was 21.4% (range 11.7-35.9). After excluding from the analysis patients who received lapatinib alone, the ORR was 29.2% (range 18.5–42.7). The median OS of patients with BM from Her2/neu-positive BC was 11.2 months (range 8.9–14.1 months), and PFS was 4.1 months (range 3.1–6.7 months) [30].

The targeted therapies and immunotherapies that have the significant efficacy for treatment on patients with BM from various malignant tumors are presented in **Table 7**.

Iuchi et al. [31] reported on 41 patients with BM from epidermal growth factor receptors (EGFR) mutant lung adenocarcinoma treated with gefitinib. Patients were assigned gefitinib 250 mg/day until the disease progression or development of unacceptable toxicity. The ORR was 87.8%, and the median OS and PFR were 21.9 months (range 18.5–30.3 months) 14.5 months (range 10.2–18.3 months), respectively [31].

Gerber and associates [32] presented the results of treatment on 110 patients with BM EGFR-mutated lung adenocarcinoma. Depending on the treatment regimen, all patients were divided into 3 groups: group 1 (n = 63) patients who received erlotinib day until the disease progression or development of unacceptable toxicity, group 2 (n = 32) was treated only WBRT, group 3 (n = 15) was treated only SRS. The median OS of all 110 patients was 33 months: 26 months in group 1 and 35 and 63 months in groups 2 and 3, respectively [32].

An open-label, single-arm, phase 2, multicenter study was performed to investigate the efficacy of vemurafenib in 146 patients with BM from BRAFV600-mutated melanoma. Patients were divided into two cohorts: cohort 1 (n = 90) patients who had not previously received BM

Name	Primary tumor type	Number of patients	Response rate	Median overall survival (months)
Gefitinib	NSCLC	41	36 (87.8%)	21.9 (18.5–30.3)
Erlotinib		63	n/a	26
Vemurafenib	MM	cohort 1–90	16 (18%)	8.9 (0.6–34.5)
		cohort 2–56	10 (18%)	9.6 (0.7–34.3)
Dabrafenib		cohort 1–89	cohort 1	cohort 1
		cohort 2–83	V600E–39%	V600E–7.6;
			V600 K–31%	V600K–3.7;
			cohort 2	cohort 2
			V600E–7%	V600E–7.2;
			V600 K–22%	V600 K–5.0;
Crizotinib	NSCLC	20	3 (15%)	10.3
Ceritinib	NSCLC	124 (ASCEND-1)	10* (36%)	n/a
		140 (ASCEND-2)	54 (38.6%)	n/a
		50 (ASCEND-3)	29 (58%)	n/a
Alectinib	NSCLC	136 (100%)	32* (64%)	n/a
		50* (37%)	37** (43%)	
		86** (63%)		
Bevacizumab + carboplatin + paclitaxel		67	42 (62.7%)	16
Trastuzumab	BC	56	n/a	10.5 (8.3–17.7)
Lapatinib		30	n/a	21.4 (12.5–27.1)
Trastuzumab + lapatinib		28	n/a	25.9 (18.5–30.1)
Ipilimumab	MM	cohort A–51	cohort A	cohort A
		cohort B–21	9 (18%)	7 (4.1–10.8)
			cohort B	cohort B
			1 (5%)	3.7 (1.6–7.3)
Ipilimumab + fotemustine	MM	20	1 (5%)	12.7 (2.7–22.7)
Pembrolizumab	NSCLC, MM	18	6 (33%)	7.7
		18	4 (22%)	n/a

n/a, not applicable.*Patients with measurable target brain lesions.

**Patients without measurable target brain lesions.

Table 7. The efficacy targeted therapy and immunotherapy in patients with brain metastasis.

local therapy (radiation therapy or surgery), and previous systemic therapy did not include BRAF or MEK inhibitors; cohort 2 (n = 6) patients with progression of melanoma BM after previous local therapy. ORR was 18% in both cohorts (16 and 10 patients in cohort 1 and 2,

respectively). The PFS was 3.7 months (range 0.03–33.4 months) in cohort 1 and 4.0 months (range 0.3–27.4 months) in cohort 2. The median OS was 8.9 months (range 0.6–34.5 months) and 9.6 months (range 0.7–34.3 months) in cohort 1 and 2, respectively [33].

An open-label, phase 2, multicenter study (BREAK-MB) was evaluated to observe the effectiveness of oral administration of dabrafenib 150 mg twice daily in 172 patients with brain parenchyma metastases from melanoma with a mutation of BRAF V600E (139 patients) and V600E (33 patients). Patients were divided into two cohorts: cohort 1 (n = 89) patients who had not previously received BM local therapy (radiotherapy or surgery), cohort 2 (n = 83) patients with intracranial progression of melanoma after previous BM local therapy. The ORR in cohort 1 was 39% and 31% in patients with mutations V600E and V600K, respectively, and in cohort 2 in 7% of patients with mutation V600E and 22% with mutation V600K. The median OS in patients with the V600E mutation was 7.6 and 7.2 months, and 3.7 and 5.0 months in patients with V600K mutation in cohort 1 and 2, respectively. The PFS was 3.7 months in patients with mutations BRAF V600E and V600K in cohort 1 and 2, respectively, and 1.8 months in patients with BRAF V600K mutation in cohort 1, and 3.8 months in patients with BRAF V600K mutation in cohort 2 [34]. Xing P. and associates (2016) presented the results of crizotinib treatment on 20 advanced ALK-rearranged NSCLC patients with baseline brain metastases in Chinese population. The median OS of patients was 10,3 months and PFS was 21,2 months [35].

The efficacy of ceritinib for the treatment of BM in patients with ALK-positive NSCLC was evaluated in the ASCEND-1, ASCEND-2, and ASCEND-3 trials. In the ASCEND-1 study, 124 patients with ALK-positive NSCLC were diagnosed with BM, 98 of the 124 patients had previously received ALK (crizotinib) inhibitor therapy prior to progression, and 26 patients without previously ALK inhibitors treatment. Only 14 patients (10 patients had received crizotinib before and 4 had not received ALK inhibitors before) had investigator-assessed brain lesions selected as target lesions at baseline. In seven of them (four patients after previous therapy with ALK inhibitors and three without previous therapy) was detected PR and in three patients discovered SD (all after previous crizotinib therapy). The PFS was 6.9 months (range 5.4–8.4 months) for all patients or 6.7 months (range 4.9–8.4 months) for patients previously treated with ALK inhibitors and 8.3 months (range 4.6–not applicable) for patients who have not previously received ALK inhibitors [36] .

Crino and co-workers [37] reported a single-arm, open-label, multicenter, phase 2 study of ceritinib in a heavily pretreated patient population with ALK-rearranged NSCLC (ASCEND-2) in 140 patients who received at least two lines of therapy including platinum-based chemotherapy and crizotinib. The ORR was 38.6% (range 30.5%–47.2). The median of follow-up time 8.8 months (range, 0.1–19.4 months) and the median PFS was 5.7 months (range 5.4–7.6 months) [37].

In ASCEND-3 trial, efficacy of ceritinib was investigated in 124 ALK-positive NSCLC patients who had not previously received therapy with ALK inhibitors. Among 124 patients included in this study, 50 patients (40%) had BM, and radiation was performed on 27 (54%) patients for brain metastatic lesions. The median PFS was 10.8 months (range 7.3–not available), and ORR was detected in 27 (54%) patients [38].

Gadgeel and assistants analyzed the results of two studies (NP28761 and NP28673) to investigate the efficacy and safety of the use of alectinib for treating patients with BM from ALK-positive NSCLC with disease progression after previous treatment with crizotinib. Measurable target brain lesions were detected in 50 (37%) patients and in 86 (63%)—without measurable target brain lesions. The disease control rate (DCR) was detected in 32 (64%) patients with measurable target brain lesions (PR = 22%) and in 37 (43%) patients without measurable target brain lesions (PR = 27%). In patients who underwent radiation therapy of BM (n = 95) before started alectinib therapy intracranial response rate (ICRR) was 35.8% versus 58.5% in patients (n = 41) who did not receive previously radiation therapy [39].

At phase II prospective, noncomparative BRAIN study investigated efficacy and safety of combination bevacizumab (15 mg/kg) + carboplatin (AUC 6) + paclitaxel (200 mg/m^2) IV every 3 weeks as the first line of treatment of non-squamous NSCLC patients (n = 67) with asymptomatic, previously untreated BM. PR and SD of intracranial metastases was recorded in 42 (62.7%) and 18 (26.9%), respectively. Median PFS was 6.7 months. (5.7–7.1), and the median OS was 16 months [40].

In the retrospective multicenter study, Yap and co-workers [41] evaluated the efficacy of anti-Her2/neu therapy in patients with BM from Her2/neu overexpression BC. Among 280 patients with BM Her2/neu-positive BC, 260 (92.9%) patients underwent radiation therapy, 160 (57.1%) patients underwent chemotherapy, and 114 (40.7%) anti-Her2/neu therapy. Of the 114 patients receiving anti-Her2/neu therapy, 56 (49.1%) patients receive trastuzumab, 30 (26.3%)—lapatinib and 28 (24.6%) trastuzumab plus lapatinib combination. The median OS was significantly higher in patients receiving combined anti-Her2/neu therapy and was 10.5 months (range 8.3–17.7 months) in the trastuzumab group, 21.4 months (range 12.5–27.1 months) in the lapatinib group, and 25.9 months (range 18.5–30.1 months) in patients from the trastuzumab + lapatinib group [41].

An open-label, phase 2 trial investigated efficacy of ipilimumab for the treatment of patients with BM from melanoma. A total of 72 melanoma patients with BM were divided into 2 cohorts: cohort A (n = 51)—patients with asymptomatic BM, cohort B (n = 21)—patients with symptomatic BM and received glucocorticoids. All patients received ipilimumab at 10 mg/kg IV every 3 weeks for a total of 4 cycles. The DCR was 18% in cohort A and 5% in cohort B. Overall survival for 1 year was 31% and 19% with a median OS 7 months (range 4.1–10.8 months) and 3.7 months (range 1.6–7.3 months) in the cohort A and B, respectively [42].

In the NIBIT-M1 study Di Giacomo and co-workers [43] reported on 20 patients with asymptomatic BM from melanoma who received combined systemic therapy of ipilimumab (10 mg/kg IV every 3 weeks for a total of 4 injections) and fotemustine (100 mg/m^2 IV weekly total 3 injections). Maintenance therapy was carried out according to the regiment: fotemustine every 3 weeks from 9 weeks of therapy and ipilimumab every 12 weeks from 24 weeks from the onset of systemic therapy to disease progression or patient failure, or to the occurrence of excessive toxicity. Maintenance therapy was carried out according to the regiment: fotemustine every 3 weeks from 9 weeks of therapy and ipilimumab every 12 weeks from 24 weeks from the onset of systemic therapy to disease progression or patient failure, or to the occurrence of excessive toxicity. Seven patients (35%) before systemic treatment were radiotherapy.

The ORR was 5% at an immunological response rate was 50%. With median follow-up of 39.9 months, the 3-year OS was 27.8%, and the median OS was 12.7 months.

Goldberg et al. [44] in non-randomized, open-label, phase 2 trial was investigated effectiveness of pembolizumab in 36 patients with asymptomatic BM from NSCLC (n = 18) and melanoma (n = 18). The PD-L1 expression in primary tumor was detected in patients with NSCLC only. All patients received pembolizumab 10 mg/kg IV every 2 weeks before disease progression. The ICRR was 33% for NSCLC and 22% for melanoma. The median follow-up was 11.6 months (range 8.5–13.9 months) and median OS was not achieved (NA) in the patients with melanoma BM. The median follow-up was 6.8 months (range 3.1–7.8 months) and median OS was 7.7 months (range 3,5–ND) in the NSCLC patients with BM [44].

6. Conclusions

In recent decades, significant progress has been made in diagnosing, predicting, and treatment of patients with BM of various malignant tumors. Nevertheless, the successes achieved are not sufficient, since the overall survival rates of patients remain low. Further studies of the mechanisms of metastasis of malignant tumors in the brain can serve as a basis for the development of methods for the prevention of BM, and the study of the role of BBB in the development of resistance to systemic therapy will help develop methods that overcome this natural barrier and increase the effectiveness of antitumor drugs. Applying a multidisciplinary approach to developing patient treatment, tactics using the current flow forecast scales will lead to a more valid appointment of radiation therapy, surgery, systemic antitumor and symptomatic therapy to preserve the neurological and neurocognitive function, and the quality of life of patients.

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