Chemotherapy in brain metastases of lung and breast cancer

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Brain metastases are the most common intracranial tumors and their incidence is increasing. Results of a recent analysis have confirmed that good performance status, control of the primary tumor, absence of extracranial disease and age less than 65 years are predictive of survival. Without treatment, patients with brain metastases survive approximately 1 month after diagnosis. Currently, chemotherapy has a limited role in the treatment of most brain metastases. Several regimens and new therapies, with a good penetration through the blood–brain barrier, such as Temozolomide (Temodar®, Shering Plough Corp.), have been used in brain metastases with different results depending on the histology of the primary tumor and on the administration schedule. A better understanding of the complex processes underlying the development of brain metastasis will enable us to develop more satisfactory targeted treatments.

Keywords:
brain metastases, chemotherapy

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Epidemiology

Brain metastases, the most common intracranial tumors, occur in 15–40% of cancer patients. The estimated incidence of brain metastasis in the USA is 170,000 new cases a year [1,2]. Cerebral metastases are less frequent in children than in adults, with an estimated incidence of 6–10% [3]. The incidence of CNS metastases has increased in recent years, probably due to the longer survival of patients given aggressive treatments for primary tumors. The frequency of brain metastases may also appear to have increased because it is now possible to detect small tumors, thanks to the improvements achieved in magnetic resonance imaging (MRI) techniques [4]. However, in a recent epidemiologic study spanning a period of 10 years, this increased incidence was not confirmed in patients with lung and breast cancer [5]. The incidence rates vary depending on differences in the type of study undertaken (autoptic or clinical), patient selection and duration of follow-up.

Lung cancer is the most common primary source of metastases to the CNS, causing brain metastases in 9.7–64% of patients. Among patients with breast cancer, the incidence of brain metastases is 2–25% and there is a clear relation between stage of disease and incidence of brain metastases [5]. The other most common form of cancer with spread to the CNS is melanoma, with an incidence of 4–20%. Metastases from cancer of the colorectal and the genitourinary tract and sarcoma, are less frequent (1%). The primary site is unknown in up to 15% of patients with brain metastases [6]. In patients with lung and breast cancer, the occurrence of brain metastases is rarer in patients aged 70 years or over. This may reflect a less aggressive diagnostic approach in the elderly population but may also be related to a less aggressive disease in older patients [5].

Pathogenesis

Brain metastases most commonly appear when the disease is disseminated, but dissemination is not a random process. Tumors tend to metastasize in certain organs and there is a specific interaction between tumor cells and the organ involved. It is now widely accepted that the metastatic process is defined by the 'seed and soil' theory: tumor cells (seed) have a specific affinity for the molecular and genetic characteristics of certain organs of the host (soil) [7]. To produce brain metastases, the tumor completes several steps, that are generalized as follows:

- Reaching the brain vasculature through a process termed intravasation
- Attaching to the endothelial cells
- Extravasating into the parenchyma
- Proliferating
- Inducing neoangiogenesis

The migration of tumor cells into blood vessels depends on the expression of invasion related molecules, such as metalloproteinases (MMPs) and on the production of enzymes that allow the cells, such as heparanases, to cross the endothelium. A circulating tumor cell exhibits its organ

specificity when it adheres to the endothelium of the target organ. Tumor cells first tend to arrest in small vessels and then to interact specifically with brain endothelial cells through the binding of specific adhesion molecules (integrins). When tumor cells adhere to the endothelium, several signaling pathways activated in the tumor cells and in the endothelium allow the tumor cells to bypass physical barriers, such as the extracellular matrix and the basal membrane. In the brain, once tumor cells cross the endothelium, they come into contact with subendothelial astrocytes that contribute to the process of tumor invasion by producing heparanase and hyaluronidase [8,9]. In the brain tissue, tumor cells interact with the microenvironment and this step in primary growth is considered to be responsible for limiting the rate of metastasization. Preclinical studies with melanoma cell lines have demonstrated that 80% of injected melanoma cells extravasate in metastatic organs but only 3% of these cells form micrometastases and only 1% form macrometastases [10–11]. At the extravasation step, brain metastatic melanoma cells produce a variety of molecules, such as basic fibroblast growth factor (bFGF), transforming growth factor (TGF) and interleukin(IL)-1β that potentially induce secretion of mitogenes by the surrounding glia [8]. The micrometastatic focus needs an adequate blood supply to grow and the triggering of this process is marked by angiogenesis, which is the result of a balance between pro-angiogenic and anti-angiogenic factors. The vascular endothelial growth factor (VEGF) plays a key role in the development of neovascularization. Metastatic foci exhibit a high production of VEGF, which is secreted into the extracellular space, binding the VEGF receptors into the endothelial cells and activating angiogenesis [7]. However, a better understanding of the complex biology of brain metastases, will allow the development of target therapies aimed at interrupting tumor–host cell interaction.

Blood–brain barrier

The microvasculature of the brain, a relatively isolated site, is lined by a continuous, nonfenestrated endothelium with tight junctions and little pinocytic vesicle activity. This structure, the blood–brain barrier (BBB), is, moreover, covered by the terminal processes of astrocytes that actively contribute to its integrity. The BBB limits the passage of circulating macromolecules into the brain parenchyma. The passage of macromolecules from the blood is regulated by:

- Passive transport – which is regulated by the physical nature of membranes, with lipid solubility being the most important determinant of BBB permeability
- Active transport – which is effected by active efflux pumps in the BBB and in the choroid plexus, that reduce the penetration of xenobiotics and endogenous substances into the brain

This structure and the lack of lymphatic vessels keep the brain in an immunologically 'privileged' site, preventing most drugs and microorganisms from entering it. Furthermore P-glycoprotein (P-gp), a drug efflux pump that plays a significant role in modulating multidrug resistance (MDR), is highly expressed in the BBB. Recent studies have demonstrated that brain metastases from melanoma and lung cancer have a lower P-gp expression than normal brain tissue, suggesting that a further MDR mechanism may be involved in brain metastases [11]. A recent analysis by Fidler and colleagues demonstrated that the permeability of the BBB to sodium fluorescein was intact in all small metastases and all secondary tumors with a diffuse growth pattern, except if the tumor-cell clusters had combined to form large masses [7]. A growing tumor mass is, in fact, associated with increased expression of VEGF, which induces the formation of new vessels. These new vessels lack the properties of those normally found in the same anatomical site and cause the increased BBB leakage [7]. Two important demonstrations against the role of BBB in brain tumors are the increased microvascular permeability in gliomas that leads to brain edema and the accumulation of the intravenous contrast during MRI or computed tomography (CT).

Treatment

Untreated patients have a median survival time of only approximately 4 weeks and nearly all die as a direct result of the brain tumor. In a retrospective study median survivals were approximately 1, 4 and 9 months following treatments with steroids, radiotherapy and surgery with radiation, respectively [12]. The Radiation Therapy Oncology Group (RTOG) analyzed 1200 patients in multiple trials and formulated a three-tiered classification scheme to predict survival in patients with brain metastases [1]. Patients with better prognosis (Class I) had all the following criteria: Karnofsky Performance Status of 70 or more, an age of less than 65 years, controlled primary tumor and no

Table 1. Recursive portioning analysis of prognostic factors in patients with brain metastases [1].

RPA Class	Prognostic factors	Median survival (months)
I	- KPS ≥ 70 - < 65 years of age - Controlled primary tumor - No systemic disease	7.1
II	- KPS ≥ 70 and at least one of the following: - ≥ 65 years of age - Uncontrolled primary tumor - Presence of systemic disease	4.2
III	- KPS < 70	2.3

KPS: Karnofsky performance status; RPA: Recursive portioning analysis.

extracranial metastases. Patients with the worst prognosis (Class III) have only Karnofsky Performance Status of less than 70. All other patients are Class II. The median survival rates for Class I, II and III patients are 7.1, 4.2 and 2.3 months, respectively (**Table 1**).

Chemotherapy in brain metastases from lung tumor

Non-small-cell lung cancer

The most common source of brain metastases is lung tumor [13]. Small cell lung carcinoma (SCLC) and adenocarcinomas have similar frequencies of metastasization (30–36%), while squamous cell carcinomas have a lesser tendency to spread to the brain. Tumors located apico-peripherally have a greater metastatic potential. Cerebral metastases from the lung are generally multiple but some studies report solitary metastases in 30–40% of cases [14]. Studies have been conducted to identify molecular markers predictive of the development of brain metastases from lung tumors. Milas and colleagues analyzed different molecules, such as epidermal growth factor receptor (EGFR), cyclooxygenase (COX)-2, BCL-2-associated X protein (BAX) but no difference was found between patients with brain metastases and those without, for EGFR, COX-2 and BAX expression [15].

Ceresoli and colleagues who analyzed the risk of cerebral metastatic disease in 112 patients with stage III non-small-cell lung cancer (NSCLC), reported that brain metastases were the first site of recurrence in 22% of patients and that in 72% of these patients the brain was the exclusive site of recurrence [16]. Elsewhere, the authors demonstrated that an age of less than 60 years was associated with an increased risk of brain metastases and a reduced time to brain recurrence, whereas the presence of bulky mediastinal lymph nodes was of borderline significance. A recent retrospective study undertaken in the same subgroup of patients reviewed the incidence and timing of diagnosis of cerebral metastases in 422 patients undergoing combined modality therapy [17]. Of the patients who developed brain metastases as a site of first relapse (20%), 46.5% developed them within 16 weeks of therapy completion. This datum demonstrates that brain metastases often developed early in the course of the treatment and this timing must be considered in the choice of treatment. Several studies have been conducted in patients with previously untreated brain metastases from NSCLC. Boogerd and colleagues treated 13 patients with teniposide alone and reported a response rate of 23% [18]. In this study, 46% of patients had previously been treated for brain metastases with surgery and/or radiotherapy. Another three studies [19–21] utilized a two-drug regimen and obtained a response rate ranging from 27–38%. Newton and colleagues administered intra-arterial carboplatin plus intravenous etoposide in nine patients with brain metastases from NSCLC, obtaining a response rate (RR) of 44% [22]. Other studies have tested the three-drug regimen, achieving a RR of 26–50% [20,23–25] (**Table 2**). Aggressive treatment with whole brain radiotherapy (WBRT), vinorelbine (Navelbine®, Kyowa Hakko), ifosfamide (Mitoxana®, Baxter Oncology) and cisplatin achieved a similar response rate of 56% in brain lesions with an important toxicity [26]. Recently, new drugs have been investigated in patients with brain metastases. Temozolomide (TMZ) presents a good penetration through the BBB and has an optimal tolerance. Several Phase II studies have

shown that TMZ alone achieved a limited response (< 9%) in brain metastases from NSCLC [27–29]. In their study of 21 patients with brain metastases from NSCLC treated with TMZ 150 mg/m^2 on days 1–7 and 15–21 every 28 days, Siena and colleagues reported, an overall response rate of 24% (partial response [PR] plus stable disease [SD]) [30]. However, Dziadziuszko and colleagues reported no objective response in stage IV patients with NCSLC treated with TMZ alone; their study was stopped prematurely and it was concluded that the single agent, TMZ, had no therapeutic benefit [31]. In two studies, TMZ was administered combined with WBRT. Antonadou and colleagues treated patients with brain metastases from solid tumors (64% NSCLC) and reported a RR of 96% in patients treated with the combination; this was significantly greater than that achieved with radiotherapy (RT) alone (67%) and a marked neurological improvement was obtained in the group receiving TMZ [32]. The overall survival of patients treated with the combined regimen (8.6 months) was not significantly longer than that of patients treated with RT alone (7 months). Unfortunately, these results refer to all histologies grouped together. Dardoufas and colleagues found an RR of 82% in 11 patients with brain metastases from NSCLC treated with TMZ plus WBRT (**Table 2**) [33]. These results have led to an increasing interest in the use of chemotherapy with radiation therapy, including an ongoing Phase III trial of TMZ and radiotherapy for NSCLC. New targeted therapies are also under investigation in response to new information regarding the metastatic process, such as targets for growth factor receptors and other protein tyrosine kinases, internal signal transduction pathways, ras activation and matrix metalloprotease activity [34–35]. Fujiwara and colleagues [36] described a patient with brain metastases from

Table 2. Chemotherapy in brain metastases from non-small-cell lung cancer.

Author	Patients	Previous treatment (% of treated patients)	Treatment	RR (%)	MST (months)	Ref.
Fujita *et al.* (2000)	30	No	CDDP, Ifo, CPT-11	50	12	[24]
Dziadziuszko *et al.* (2003)	12	No chemotherapy WBRT	TMZ	0	NR	[31]
Cortes *et al.* (2003)	26	No	Paclitaxel, CDDP and either VNR or GEM	38	5	[25]
Boogerd *et al.* (1999)	13	WBRT (23%) Surg. + WBRT (23%)	VM-26	23	NR	[18]
Robinet *et al.* (2001)	76	No	CDDP, VNR	21	5	[20]
Bernardo *et al.* (2002)	22	No	VNR, GEM, CBDCA	45	7	[23]
Crinò *et al.* (1999)	155/152	No	Mito, Ifo, CDDP vs. GEM, CDDP	26 vs. 38	9.6 vs. 8.6	[19]
Newton *et al.* (2003)	9	Chemotherapy (67% for all histologies) WBRT (100%)	i.a. CBDCA i.v VP-16	44	4 (for all histologies)	[22]
Franciosi *et al.* (1999)	43	No	CDDP, VP-16	30	8	[21]
Siena *et al.* (2003)	21	NR	TMZ	24 (PR +SD)	NR	[30]
Christodoulou *et al.* (2001).	12	Heavily pretreated	TMZ	8	(4 for all histologies)	[27]
Friedman *et al.* (2003)	29	WBRT (100%)	TMZ	7	NR	[28]
Abrey *et al.* (2001)	22	WBRT (100%) Chemotherapy (85% for all histologies)	TMZ	9	(7 for all histologies)	[29]
Dardoufas *et al.* (2001)	11	NR	WBRT + TMZ	82	NR	[33]

CBDCA: Carboplatin; CDDP: Cisplatin; CPT-11: Irinotecan; GEM: Gemcitabine; i.a.: Intra-arterial; Ifo: Ifosfamide; i.v.: Intravenous; mito: Mitomicina; MST: Median survival time; RR: Response rate; surg.: Surgery; TMZ: Temozolomide; VM-26: Teniposide; VNR: Vinorelbine; VP-16: Etoposide; vs.: Versus; WBRT: Whole brain radiotherapy.

Table 3. Chemotherapy in brain metastases from small cell lung cancer.

Author	Patients	Previous treatment (% of treated patients)	Treatment	RR (%)	MST (months)	Ref.
Postmus *et al.* (2000)	60 vs. 60	Chemotherapy (43%/44%)	VM-26 vs. VM-26 + WBRT	22 vs. 57	3.2 vs. 3.5	[39]
Postmus *et al.* (1995)	80	Chemotherapy (69%) WBRT (14%) PCI (13%)	VM-26	33	NR	[43]
Groen *et al.* (1993)	20	Chemotherapy (35%) WBRT (5%) PCI (10%) WBRT + CT (50%)	CBDCA	40	3	[41]
Korfel *et al.* (2002)	30	Chemotherapy (100%) WBRT (27%)	Topotecan	33	3.6	[42]
Fujita *et al.* (2000)	12	Chemotherapy	CDDP, Ifo, CPT-11	92	NR	[44]
Newton *et al.* (2003)	2	Chemotherapy WBRT (100%)	i.a. CBDCA i.v. VP-16	0	4 (for all histologies)	[22]
Christodoulou *et al.* (2001)	5	Heavily pretreated	TMZ	0	4 (for all histologies)	[27]

CBDCA: Carboplatin; CDDP: Cisplatin; CPT-11: Irinotecan; CT: Chemotherapy; i.a.: Intra-arterial; Ifo: Ifosfamide; i.v.: Intravenous; MST: Median survival time; PCI: Peritoneal cancer index; *RR: Response rate; surg.: Surgery; TMZ: Temozolomide; VM-26: Teniposide; VP-16: Etoposide, vs.: Versus; WBRT: Whole brain radiotherapy.*

NSCLC with a marked tumor regression after a week of therapy with ZD1839 (Iressa®, AstraZeneca). Moreover, Cappuzzo and colleagues reported that four patients with brain metastases from NSCLC refractory to standard therapy responded to ZD1839 therapy; the authors obtained one complete response and three partial responses after 3 months of therapy [37,38].

Small cell lung cancer

Approximately 10% of SCLC patients present with brain metastases at the time of the diagnosis and over 50% will develop symptomatic brain metastases in the following period [39]. Kristensen and colleagues reviewed 12 studies that included 71 patients with brain metastases at the primary diagnosis (chemonaïve group) and 45 patients with brain relapse (chemotreated group) treated with different chemotherapeutic regimens [40]. Three studies, analyzed in the chemonaïve group, also included cranial irradiation but the RR was assessed before irradiation. In the chemonaïve group, the RR to different chemotherapeutic regimens was 76%, which included 32% of complete responses (CRs); no major difference was found between the survival of patients with or without radiotherapy consolidation. Brain metastases from previously chemotreated SCLC patients achieved an RR of 43%. The Kristensen review suggests that brain metastases from SCLC at initial diagnosis respond as well as extracranial disease to systemic chemotherapy [40]. More recent studies (**Table 3**) evaluated the response of brain metastases of pretreated patients to a monochemotherapy regimen with different agents and reported a RR ranging from of 33–40% [41–43]. Fujita and colleagues treated 12 patients who were refractory to treatment or had progressive brain metastases from SCLC with a multi-agent regimen and reported an RR of 92% [44]. Postmus and colleagues compared single agent teniposide chemotherapy with combined chemotherapy plus WBRT [39]. The combined modality achieved a much higher RR (57 vs. 22%) in patients with brain metastases and a longer time to progression of brain metastases than teniposide alone. However, these data do not correlate with an improvement in overall survival, probably due to a high failure rate in extracranial sites. The efficacy of TMZ in SCLC has been tested in at least two studies. Christodoulou and colleagues administered TMZ in five heavily pretreated patients with brain metastases from SCLC, without obtaining any response [27]. In another study, a Phase II randomized trial, Antonodau and

colleagues administered TMZ in combination with WBRT in patients with brain metastases from solid tumors (19% SCLC) and, reported a very high RR: 96% in patients treated with the combination and 67% in those treated with RT alone [32]. These results refer to patients with different types of primary tumor (NSCLC 65%, SCLC 19%, breast cancer 10%, unknown 6%) and no division into groups being made on the basis of histology.

Chemotherapy in brain metastases from breast cancer

Between 22–25% of brain metastases originate from primary breast tumors, cerebral involvement occurring in 10–15% of patients with advanced breast cancer. Most patients are young and brain metastases develop when the primary disease is at a late state, probably because chemotherapeutic agents used for breast carcinoma do not penetrate the BBB [14,45]. Boogerd and colleagues reviewed 137 patients with brain metastases and at multivariate analyses found that survival was significantly longer in patients without manifest systemic disease, with single brain metastases, with neurologic symptoms present for more than 4 weeks prior to diagnosis and in those treated with chemotherapy after diagnosis [46]. In the same study, CNS metastases was the cause of death or a major contributing factor to it in 68% of the patients, indicating the need for improvement of the treatment of brain metastases itself. A recent epidemiological study, conducted in 802 patients with breast carcinoma over a period of 10 years did not observe any increase in the incidence of brain metastases [5]. In patients with brain metastases from breast cancer, four Phase II trials demonstrated a response rate of 38–58% with a variety of multi-agent regimens including cisplatin or carboplatin and etoposide, anthracyclines, cyclophosphamide, methotrexate, cisplatin and 5-fluorouracil (**Table 4**). The treatment with TMZ alone or in combination with WBRT was exploited in different studies, also in patients with breast cancer, with an overall response (OR) of 0–44% (**Table 4**). Many new cytotoxic drugs used alone or in combination have shown some activity in

Table 4. Chemotherapy in brain metastases from breast cancer.

Author	No. of patients	Previous treatment (% of treated patients)	Treatment	RR (%)	MST (months)	Ref.
Cocconi *et al.* (1990)	22	Chemotherapy (73%) WBRT (9%)	CDDP, VP-16	55	13	[63]
Boogerd *et al.* (1993)	22	Chemotherapy (32%) WBRT (32%)	CMF or FEC	58	6	[46]
Rosner *et al.* (1986)	100	Chemotherapy (63%)	Various	50	NR	[63]
Franciosi *et al.* (1999)	56	Chemotherapy (50%)	CDDP, VP-16	38	8	[21]
Newton *et al.* (2003)	9	Chemotherapy (67% for all histologies) WBRT (100%)	i.a. CBDCA, i.v. VP-16	55	4 (for all histologies)	[22]
Siena *et al.* (2003)	21	NR	TMZ	19 (PR + SD)	NR	[30]
Christodoulou *et al.* (2001)	4	Heavily pretreated	TMZ	0	(4 for all histologies)	[27]
Friedman *et al.* (2003)	15	WBRT (100%)	TMZ	0	NR	[28]
Abrey *et al.* (2001)	10	WBRT (100%) Chemotherapy (85% for all histologies)	TMZ	0	(7 for all histologies)	[29]
Martinez-Cedillo *et al.*(2003)	16	NR	WBRT + TMZ TMZ	44%	12	[64]
Dardoufas *et al.* (2001)	3	NR	WBRT + TMZ TMZ	0%	NR	[33]

CBCDA: Carboplatin; pts: patients; CDDP: cisplatin; CMF: cyclophosphamide, methotrexate, 5-fluorouracil; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; MST: median survival time; PR: Partial response; RR: response rate; SD: Stable disease; TMZ: temozolomide; VP-16: etoposide; vs.: versus; WBRT: Whole brain radiotherapy.

breast cancer. Wang and colleagues reported a case of a prolonged PR to capecitabine with an improvement in Performance Score in one patient with brain metastases from breast cancer progressed after WBRT, hormonal treatment and systemic chemotherapy that included 5-fluorouracil [47]. The taxanes, in particular, are one of the most active new agents. However, some studies demonstrated a high incidence of CNS relapse in patients with a systemic response to regimens containing taxanes. In their review of a series of 152 patients treated with paclitaxel (Taxol®, Bristol-Myers Squibb) in five Phase II trials at the Memorial Sloan Kettering Cancer Center (MSKCC), Freilich and colleagues found that 53 patients (35%) had a partial or CR, 25 had a minor response and 52 of the 78 patients who responded to paclitaxel (67%) had subsequent disease progression with six of these (12%) demonstrating isolated CNS involvement while maintaining a systemic response [48]. Crivellari and colleagues demonstrated that 30% of patients with metastatic or locally advanced breast cancer treated with epirubicin (Pharmorubicin®, Pharmacia) and docetaxel (Taxotere®, Aventis Pharma) developed CNS metastases [45]. Disease progression in the CNS alone was observed in 39%. Two other Phase I trials containing taxanes reported isolated CNS relapse rates of 9 and 20%, respectively, while maintaining partial remission of systemic disease [49,50]. Furthermore, Schwonzen and colleagues treated 21 breast cancer patients with liposomal doxorubicin and paclitaxel and observed a 24% rate of metastases to the brain [51]. Two other reports showed an increased incidence of metastasis to the brain as the first site of recurrence in breast cancer patients treated with adjuvant chemotherapy, with respect to untreated controls (12.8 vs. 0% and 7.4 vs. 1.2%, respectively) [52,53]. These data suggest that adjuvant chemotherapy did not penetrate the CNS, allowing the development of brain metastases in a sanctuary site. Paclitaxel is a water-soluble agent, that does not cross the BBB under normal conditions but it may have a greater penetration into the tumor when the barrier is disrupted, as indicated by contrast enhancement in MRI. It is probable that treatment with chemotherapy that does not normally cross the BBB resulted in longer disease-free intervals, allowing the growth of cancer cells already present in the CNS at diagnosis.

Recently, an increased incidence of brain metastases has been reported in women receiving trastuzumab (Herceptin®, Roche)-based chemotherapy. Bendell and colleagues reported that 34% of patients receiving trastuzumab-based chemotherapy develop brain metastases, often while their other systemic tumor burden was clinically responding [54]. In this study, patients who received trastuzumab as first line therapy for metastatic disease had a greater risk (42%) of developing CNS metastases. Wardley and colleagues [55] evaluated the incidence of brain metastases in 33 metastatic breast cancer patients receiving trastuzumab and found that the incidence of CNS metastases was 33%; of the patients who developed CNS disease on trastuzumab, 15% had stable or responding disease in other sites. A high incidence of brain metastases (18.2%) was also observed in 22 patients with locally advanced or metastatic breast cancer treated with a neoadjuvant chemotherapy based on trastuzumab and docetaxel [56]. On the contrary, Lower and colleagues reported that patients receiving trastuzumab therapy were as likely as control patients to develop brain metastases (25 vs. 31%) [57]. However, firm conclusions cannot be drawn from the small series of published studies. The increased incidence of brain metastases in patients treated with trastuzumab may be related to the low penetration of trastuzumab through the BBB, which restricts the entry of large molecules into the brain. This restriction by the BBB may lead to a 300-fold lower concentration of trastuzumab in cerebrospinal fluid compared with serum concentration [58]. The increased incidence could be related to different biological properties of the HER-2 positive breast cancer. This form of cancer is highly aggressive and trastuzumab may change its natural history, prolonging survival long enough for brain complications to develop. Furthermore, the survival of patients with HER-2-positive brain metastases may be shorter because HER-2 overexpression is associated with a decreased survival in patients with metastatic breast cancer [59]. However, some studies have demonstrated that metastatic tumor may present a discordant HER-2 expression compared with primary tumor [60]. Grossi and colleagues reported that the direct intracerebral infusion of trastuzumab in a rat model provided a significant survival advantage over an equivalent dose of trastuzumab delivered systemically, without inducing significant toxicity

[61]. Thus, direct administration of trastuzumab into the tumor bypasses the BBB and delivers high concentrations of the therapeutic agent to the tumor site while minimizing systemic exposure.

Expert opinion

The therapeutic approach to brain metastases should be based on several parameters, such as the assessment of prognostic variables, the extension of neurologic and systemic disease, the histology type and its chemosensitivity. The approach will vary from aggressive treatment with chemotherapy alone or in combination with RT, for patients with highly chemoradiosensitive tumors to palliative care for patients with multiple brain metastases and an uncontrolled systemic disease. Brain metastasis is a highly selective process and a better understanding of this complex interplay will allow new targeted therapies specific to this condition to be developed.

Outlook

In the last 5 years some studies have pointed out two major questions.

- Why the frequency of CNS metastases has increased? – There is some evidence that the frequency of CNS metastases is increasing, probably due to the longer survival of patients because of more aggressive treatment of the primary tumor, even if it does not cross the BBB. The use of MRI may also have contributed to a higher detection rate. Controversially, a recent study, analyzing 2724 patients with different solid tumors did not find any evidence of increasing incidence of brain metastases [5]. These differences can be due to the method used to select the patients (Cancer Registry or autoptic series) and to the duration of follow-up. However, in the absence of definitive conclusions about incidence of brain metastases in solid tumors, a careful evaluation in the development of any neurologic symptom in patients treated with chemotherapy must be done. Remarkably, some authors propose the use of prophylactic cerebral treatment in breast cancer patients with a complete systemic response. This is particularly important, in view of the median survival after CNS progression (3 months) and this treatment should be investigated in randomized clinical trials [45].
- Has the increasing number of chemotherapeutic studies in patients with brain metastases modified the clinical approach to these patients? – At present chemotherapy alone has a limited role in the treatment of brain metastases. Chemotherapy combined with RT has probably failed to increase the survival of these patients, achieving only a modest increase in the response rate and improvement in neurologic functions.

Highlights

- **Epidemiology:** Lung cancer is the most common primary source of metastases to the CNS, causing brain metastases in 9.7–64% of patients. Among patients with breast cancer, the incidence of brain metastases is 2–25% and there is a clear relation between stage of disease and incidence of brain metastases.
- **Blood–brain barrier:** Two important demonstrations against the role of the blood–brain barrier (BBB) in brain tumors are the increased microvascular permeability in gliomas that lead to brain edema and the accumulation of the intravenous contrast during MRI or computed tomography.
- **Prognosis:** Untreated patients have a median survival time of approximately 4 weeks. Median survivals were approximately 1, 4 and 9 months following treatments with steroids, radiotherapy and surgery with radiation, respectively.
- **Brain metastases from non-small-cell lung cancer (NSCLC) chemotherapy:** Several studies have been conducted in patients with brain metastases from NSCLC. Teniposide alone, two drugs regimens and three drug regimens obtained a response rate of 23%, 21–38% and 26–50% respectively. While temozolomide (TMZ) alone or in combination with whole brain radiotherapy (WBRT) achieved a response rate (RR) of 0–9% and 82% respectively. The role of TMZ concomitant to WBRT remains to be established.
- **Brain metastases from small-cell lung cancer (SCLC) chemotherapy:** Brain metastases from SCLC at initial diagnosis respond as well as extracranial disease to systemic chemotherapy. Single agent chemotherapy obtained a RR of 33–40%. While multi-agent chemotherapy achieved a RR of 92%.
- **Brain metastases from breast cancer chemotherapy:** Phase II trials demonstrated a RR of 38–58% with a variety of multi-agent regimens including cisplatin or carboplatin and etoposide, anthracyclines, cyclophosphamide, methotrexate, cisplatin and 5-fluorouracil. TMZ alone or in combination with WBRT was exploited in different studies, with an overall response of 0–44%. However, the role of concomitant WBRT and TMZ remains to be defined. Some studies demonstrated a high incidence of CNS relapse in patients with a systemic response to regimens containing taxanes or trastuzumab.

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