Cancer Treatment Reviews 40 (2014) 716–722

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

# Indications and limitations of chemotherapy and targeted agents in non-small cell lung cancer brain metastases

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ARTICLE INFO

*Article history:*
Received 4 February 2014
Received in revised form 20 March 2014
Accepted 30 March 2014

*Keywords:*
Brain metastasis
Non small cell lung cancer (NSCLC)
Driver oncogenes
Stereotactic radiotherapy
Targeted treatment

ABSTRACT

Lung cancer is characterized by the highest incidence of solid tumor-related brain metastases, which are reported with a growing incidence during the last decade. Prognostic assessment may help to identify subgroups of patients that could benefit from more aggressive therapy of metastatic disease, in particular when central nervous system is involved. The recent sub-classification of non-small cell lung cancer (NSCLC) into molecularly-defined "oncogene-addicted" tumors, the emergence of effective targeted treatments in molecularly defined patient subsets, global improvement of advanced NSCLC survival as well as the availability of refined new radiotherapy techniques are likely to impact on outcomes of patients with brain dissemination. The present review focuses on key evidence and research strategies for systemic treatment of patients with central nervous system involvement in non-small cell lung cancer.



## Incidence and prognosis of lung cancer brain metastases

Lung cancer is characterized by a high incidence of central nervous system metastases, with 40% of patients developing brain metastases in the course of their disease [1,2]. Altogether, 40–50% of all cancer-types brain metastases originate from lung [3]. The incidence of brain metastases seems to have increased over the last years [4,5]. This phenomenon might be due in part to the effectiveness of drugs that poorly penetrate the blood–brain barrier: increased survival in patients allows for micrometastases to become symptomatic later in the course of the disease. Prognosis of non-small cell lung cancer (NSCLC) patients with brain metastases is poor, with a median overall survival (OS) time of 7 months, and a 1-year survival rate of 20% in one large series [6], with however a marked heterogeneity in outcome. Other reports tend to describe worse outcome data (typically 3–6 months), depending on patient selection and institutional profile. Graded prognostic assessment allows for a better estimate of survival time, and may help identifying subgroups of patients that could benefit from a more aggressive therapeutic approach. In this context, performance status was shown to be predictive for OS in all cancer types, whereas presence or absence of extracranial metastases is specifically prognostic in NSCLC. As a consequence, aggressive treatment for brain metastases in lung cancer patients may not be warranted in those patients presenting with a widespread metastatic dissemination outside of the central nervous system [6]. Further prognostic factors include age and control of the primary tumor. In addition, OS of patients with liver metastases was shown to be significantly shorter [7].

Whole-brain radiation therapy (WBRT) with doses up to 30 Gy has been defined as the cornerstone treatment for brain metastases from NSCLC for decades [8]. In recent years, management of brain metastases has been refined, and now includes local therapies such as surgical resection for single brain lesions, and radiosurgery for oligometastatic disease, both resulting in improved survival in better prognosis patients when compared to WBRT alone [9–11]. On the other hand, systemic therapy also remains an essential treatment strategy of disseminated NSCLC. This article will review current indications and limitations of chemotherapy and targeted agents, alone, combined or in sequence with other treatment modalities, in the management of NSCLC brain dissemination, and in the context of developments in the field of radiotherapy.

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http://dx.doi.org/10.1016/j.ctrv.2014.03.005
0305-7372/

## The relevance of the blood brain barrier

Systemic therapy for the treatment of brain metastases has been hampered by the prevailing belief that the brain is a sanctuary site: the blood–brain barrier (BBB) prevents the passage of noxious substances, and only allows small lipid-soluble molecules to cross. As a result, most chemotherapeutic agents do not cross the intact barrier, and relevant liquor permeability is known mainly for temozolomide, methotrexate and topotecan [12–14]. Anatomically, the BBB consists of a continuous endothelium with tight junctions and no fenestration, surrounded by a basement membrane, in turn covered by the podocytes of astrocytes interposed between blood vessels and neurons [15]. Efflux membrane transporters are highly expressed in endothelial cells and actively contribute to the barrier effect [16]. Tumor neoangiogenesis in brain metastases leads to newly developed blood vessels that lack the anatomical and physiological properties of the BBB [17]. When brain metastases reach a given tumor size, accompanied by the required neovessels, the BBB is disrupted. This phenomenon is readily recognized by enhancement upon intravenous contrast medium injection during magnetic resonance imaging (MRI) or computed tomography (CT). Interestingly, drug concentrations are lower in the periphery of the tumor than in the centre, suggesting a better penetration where the BBB damage is more pronounced as compared to the actively growing invasive edge [18]. While this paradigm allows for upfront use of systemic therapy in patients with macroscopic brain metastases, it also explains the frequently encountered clinical situations where the central nervous system is the first site of relapse following curative systemic therapy or brain progression using palliative systemic agents that do not sufficiently penetrate through an intact BBB.

## Chemotherapy for the treatment of brain metastases

A number of prospective trials in NSCLC patients (Table 1) have demonstrated the activity of first-line chemotherapy for brain metastases of NSCLC, with response rates ranging from 23% up to 50% for cisplatin containing combinations [19–27]. Systemic response rates were shown to correlate with intracerebral response rates, however with slightly higher systemic rates. These results demonstrate that effective cytotoxic drug combinations result in intracerebral responses, and suggest that systemic treatment should be chosen on the basis of tumor chemosensitivity rather than the theoretically expected BBB penetration.

In pre-treated patients, whether they were previously exposed to chemotherapy or radiotherapy, chemotherapy seems to play a more limited role. A retrospective analysis of single-agent pemetrexed suggested a clinical benefit (as defined by disease control encompassing responses or stabilizations) in second- and further-line in radiotherapy-naïve patients or patients with clear cerebral progression after WBRT [28]. Single-agent temozolomide has been extensively studied in patients with recurrent or progressive brain metastases. In patients who had previously undergone WBRT, temozolomide achieved a 8–9% intracranial response rate [29,30]. Disease control was reported in 41% of patients, half of them suffering from NSCLC, and resulted in neurologic improvement in 37% of patients. In another study, temozolomide treatment did not result in objective responses, either intracerebral nor extracerebral, in previously untreated patients [31].

Two randomized phase II trials compared temozolomide given concurrently with WBRT to WBRT alone in previously untreated patients, with conflicting results: both trials showed an improved overall response rate in the combination arm, resulting in a benefit in progression free survival in only one trial [32,33]. A similarly designed phase III trial, closed early due to slow patient accrual after enrolment of only 95 of 550 planned patients, showed no significant difference in CNS progression-free survival or OS between the two treatment arms [34]. The role of temozolomide remains therefore unproven. Other agents tested as adjuncts to WBRT include carboplatin, cisplatin, 5-FU, vinorelbine and topotecan, and none has shown an improvement in either response rate or OS [25,35,36].

How to sequence radiotherapy and chemotherapy in the context of multiple brain metastases remains debated. There is little prospective data to guide the choice of initial treatment strategy, with an open debate regarding the rationale for upfront chemotherapy. Concurrent WBRT and chemotherapy result in a higher likelihood of brain toxicity, particularly neurocognitive deficits [37,38]. Sequential treatment is thus considered in most patients suitable for both treatment modalities. In a preliminary report of a phase II trial presented at the American Society of Clinical Oncology meeting in 2006, patients with multiple brain metastases from NSCLC were randomly assigned to temozolomide or WBRT. After eight weeks, significantly more patients treated with temozolomide had progressed (49 of 104 versus 28 of 104 treated with WBRT). In a randomized pilot trial involving 48 neurologically asymptomatic patients, no significant differences in response rate or survival were observed when patients were treated with chemotherapy (vinorelbine/gemcitabine) followed by RT as compared to RT followed by chemotherapy. Although the number of patients in this trial is limited, the results suggest that patients with minimal or no neurological symptoms can be treated with primary chemotherapy alone without compromising their clinical outcome [39]. A phase III trial comparing early concurrent versus delayed WBRT in patients receiving cisplatin-based chemotherapy suggests that the timing of WBRT does not influence survival of NSCLC patients with brain dissemination [25]. In conclusion, chemotherapy is a reasonable first-line treatment option in patients who present with stage IV lung cancer and asymptomatic brain metastases. In this setting, upfront systemic standard platinum-based combination chemotherapy rather than standard WBRT has been proposed as an alternative. This strategy has been endorsed as an option by the European Society of Medical Oncology guidelines [8]. Surgical resection of single brain metastases and radiosurgery

**Table 1**
Selected trials studying the activity of chemotherapy in NSCLC with brain metastases.

| Author (Ref.) | *N* | Tumor type | Prior treatment | Treatment | Brain RR (%) | MST (months) |
|---|---|---|---|---|---|---|
| Cortes et al. [19] | 26 | NSCLC | No | Cisplatin/paclitaxel/vinorelbine or gemcitabine | 38 | 5 |
| Fujita et al. [21] | 30 | NSCLC | No | Cisplatin/ifosfamide/irinotecan | 50 | 12.7 |
| Cotto et al. [23] | 31 | NSCLC | No | Cisplatin/fotemustine | 23 | 4 |
| Minotti et al. [20] | 23 | NSCLC | No | Cisplatin/teniposide | 35 | 5 |
| Bernardo et al. [24] | 22 | NSCLC | No | Carboplatin/vinorelbine/gemcitabine | 45 | 7 |
| Franciosi et al. [22] | 43 | NSCLC | No | Cisplatin/etoposide | 37 | 8 |
| Robinet et al. [25] | 76 | NSCLC | No | Cisplatin/vinorelbine | 27 | NA |
| Barlesi et al. [26] | 43 | NSCLC | No | Cisplatin/pemetrexed | 41.9 | 7.4 |
| Bailon et al. [27] | 26 | NSCLC | No | Carboplatin/pemetrexed | 30 | 9.1 |