Brain metastases in patients with non-small cell lung cancer: focus on the role of chemotherapy

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introduction

Lung cancer is the leading cause of cancer-related death in many countries. Non small cell lung cancer (NSCLC) represents about 85% of lung cancer [1]. Approximately 30–40% of patients with NSCLC present with metastases, which have a preferential localization to the liver, bones, adrenal glands and central nervous system (CNS) [2]. Brain metastases are a frequent finding in patients with NSCLC and may develop in 20–40% of cases during the course of the disease [3]. Two-thirds of these patients become symptomatic during their lifetime, so brain metastases are a significant cause of morbidity and mortality. The increasing incidence of brain metastases is directly related to the improvements in the treatment of systemic disease, the consequent prolonged survival and the advances in neuroimaging. The most common mechanism of metastases to the brain is by hematogenous spread [3].

prognosis and treatment options

Brain metastases often lead to serious deterioration in neurologic and neurocognitive function. In most patients, such brain metastases are not diagnosed until signs and symptoms arise. The symptoms correlated to brain metastases are non-specific such as headache, a change in mental status, focal or generalized seizures or localized weakness [2]. Consequently the prognosis for patients with brain metastases is associated with poor outcome. The management of patients with brain metastases with NSCLC has improved over time, due to the development of new treatment options and a better knowledge of prognostic factors. Nevertheless, the diagnostic and therapeutic approach depends on a careful evaluation of the number and the extent of brain lesions, as well as an understanding of patient characteristics and the stage of the cancer, that are important determinants of prognosis. Actually, good performance status, a stationary primary tumour, the only presence of intracranial metastases and age less than 65 years determine a better prognosis [4].

Brain metastases may present as a single lesion or as multiple lesions and can be divided into three groups: solitary metastases with controlled or controllable primary disease, oligometastatic disease (fewer than three metastases) and multiple metastases [5]. The treatment approach change in the different groups and the goal is to improve both the quality and duration of the patient’s life. Whole brain radiotherapy, surgical resection or radiosurgery, stereotactic radiotherapy, brachytherapy and chemotherapy are the available options. Multi-modality strategies for treatment of brain metastases from NSCLC should be better investigated, in order to improve the outcome of these patients. Medical therapy typically includes the use of corticosteroids and antiepileptic medications, used for palliation of mass effect and seizures, respectively.

chemotherapy

The use of chemotherapy for brain metastases has been viewed historically with scepticism and usually reserved as a salvage therapy. As a single modality it has demonstrated limited efficacy and integrated therapies improve the management of patients with brain metastases. Nevertheless, it may have a greater role for patients with active systemic disease or contraindications to the other therapeutic modalities. Several chemotherapeutic agents have activity against NSCLC. These regimen would seem to be candidates for treating brain metastases, but the blood brain barrier (BBB) restricts the passage of these large, water-soluble molecules and the therapeutic drug concentrations are difficult to achieve [6]. Until 10 years ago the BBB was thought to be relatively impenetrable to chemotherapy. According to this concept of the brain as pharmacological sanctuary site, the drugs do not penetrate the intact BBB. Nevertheless, micrometastases (<1 mm) have an intact BBB, on the other hand it is partially disrupted in brain metastases >1 mm in size, as indicated by the images of CT or MRI. But patient with brain metastases frequently receive corticosteroids, which reestablishes the BBB integrity [7]. Other factors may also contribute to the failure of chemotherapy for brain metastases. Actually, NSCLC is usually chemoresistant and patients who develop brain metastases have often been heavily pretreated with chemotherapy.

Moreover, the appearance of brain metastases is often due to the failure of primary chemotherapeutic agents to control systemic disease [8]. The choice of agents and the aggressive use depends on the status of systemic disease and the patient’s prognosis. Higher response rates are observed when chemotherapy-naive patients are treated. Recent evidence suggest that the chemosensitivity of the primary tumour characterize the response to systemic treatment of brain metastases [9], but it is important to assess the most active drugs and combinations. Ideally, a chemotherapeutic agent for
brain metastases should have good BBB penetrations and a good activity against the systemic disease. Unfortunately, few treatments have both attributes. Most evidence to support the use of chemotherapy in brain metastases comes from nonrandomized trials, retrospective studies and case reports.

**monotherapy approaches**

Few single agents have shown modest activity in brain metastases for NSCLC. CDDP is one of the most active single drugs in non small cell lung carcinoma and seems to be very useful in cerebral metastases from NSCLC. Kleibauer et al. documented that 30% of patients treated with the total dose of CDDP (200 mg/m²) divided into five equal daily fractions, present an objective response with low toxicity [10].

Boogerd et al. [11] demonstrated a 23% objective response rate with teniposide in 13 patients with brain metastases from NSCLC. The activity of etoposide was valued by the Groupe Français Pneumo-Cancerologie and an objective response had observed in 4 of the 14 patients with brain metastases from NSCLC [12].

A phase II study was designed to evaluate the role of fotemustine as single drug chemotherapy in NSCLC. Two objective responses were observed among the 12 patients with evaluable brain metastases and toxicity is moderate and manageable [13].

Topotecan is a new active drug in the treatment of lung cancer and a phase I study showed its activity in advanced NSCLC, but response rates for brain metastases were not reported. Nevertheless the authors indicated that topotecan plus WBRT was a ‘tolerable’ regimen with high response rates of brain metastases [14]. However, the role of topotecan in NSCLC must be developed in further trials.

**temozolomide: from monotherapy to combination therapy**

There have been several phase II studies on the effects of temozolomide on brain metastases from different cancer such as NSCLC. It is a novel second generation alkylating agent, orally bioavailable, with a good safety profile that has a good penetration through the blood brain barrier and a limited toxicity. In these studies response ranging is from 0% to 9% [15–19], at a dosage range of 150 to 200 mg/mq/d × 5 days every 28 days. Temozolomide crosses the BBB and has a favourable toxicity profile that allows for use with radiation and other agents. Several randomized phase II trials have suggested a benefit from chemoradiotherapy with TMZ compared with WBRT alone. These results led to a phase III trial to investigate the role of TMZ plus WBRT versus WBRT alone. Interim results demonstrated an improved response rate in the experimental arm (33% versus 33%) [20]. In a trial of temozolomide, in combination with gemcitabine/cisplatin or gemcitabine/vinorelbine in patients with brain metastases from NSCLC, three of eight patients achieved a complete remission [12]. New perspectives may derive from these data to improve the treatment of advanced NSCLC.

**other combination chemotherapy regimens**

Other active molecules in advanced NSCLC have been valued in brain metastases. For example paclitaxel and cisplatin are considered a standard combination in metastatic NSCLC.

Cortes and colleagues [21] have investigated the role of this association with vinorelbine or gemcitabine as front-line therapy in brain metastases from NSCLC. The good results obtained (intracranial response rate in 38% of patients) suggest the efficacy of this combination in this setting. Several studies have reported on the use of chemotherapy combination for the treatment of brain metastases from NSCLC (Table 1).

Although systemic chemotherapy has not demonstrated a survival benefit, advances with chemotherapy may permit a re-examination of its role in this setting.

**the role of new biological drugs**

An interesting field of investigation is the efficacy of biological drugs on brain metastases from NSCLC. Gefitinib is the first molecularly targeted agent to be registered for advanced NSCLC. A number of case reports suggest that gefitinib has clinical activity against brain metastases of NSCLC [2, 27–30]. These data provide evidence that gefitinib has marked anti-tumour activity in patient with NSCLC and brain metastases, but the effect may be transient.

Actually brain metastases may become resistant to this agent more rapidly than primary lesions, but further clinical studies are required to confirm the use of gefitinib in this clinical setting [2]. Thalidomide, an immune modulator with anti-angiogenic effects, should seem to have an interesting activity in brain metastases from NSCLC. Hada and Horiiuchi [31] report a case of lung cancer patient with brain metastases who had been treated with thalidomide, celecoxib and gemcitabine, after which brain metastases have almost completely disappeared. So, this combination may play an important role for patients with NSCLC and brain metastases.

**conclusions**

In spite of the improvements in the management of patients with brain metastases, the median survival remains poor [4]. For the future changes new clinical trials are necessary to define the role of chemotherapy as prophylaxis for micrometastatic disease, as first or second line treatment and in multimodality therapy, above all in association to radiotherapy, that should become the standard treatment.

**Table 1. Combination chemotherapy for brain metastases from NSCLC**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Response rate (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPDC-FuHu [22]</td>
<td>39</td>
<td>13%</td>
<td>6</td>
</tr>
<tr>
<td>Carboplatin + Etoposide [23]</td>
<td>18</td>
<td>17%</td>
<td>7.5</td>
</tr>
<tr>
<td>Cisplatin + Etoposide [24]</td>
<td>43</td>
<td>30%</td>
<td>8</td>
</tr>
<tr>
<td>Cisplatin + Teniposide [25]</td>
<td>23</td>
<td>35%</td>
<td>5</td>
</tr>
<tr>
<td>Cisplatin + Fotemustine [26]</td>
<td>31</td>
<td>23%</td>
<td>4</td>
</tr>
</tbody>
</table>
Further studied are needed to better evaluate the pharmacokinetic properties of the different drugs in relation to central nervous system and their action in brain metastases. In this palliative setting limited life expectancy, presence of the blood brain barrier and the high drug toxicity limit the use of aggressive therapies. Consequently, the most relevant endpoints are quality of life and functional benefit of patients.

Actually, it is no use putting years into life unless you put life to those years.

references

4. Langer CJ and Mehta MP. Current management of brain metastases, with a focus on systemic options. J Clin Oncol 2005 Sep 1; 23(23).