Evaluation of Late Neurologic Adverse Events in Patients with Brain Metastases from Non-small Cell Lung Cancer

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Abstract. Aim: The purpose of this prospective evaluation was to assess the late neurologic adverse events and Karnofsky performance status (KPS) in patients with at least two brain metastases from non-small cell lung cancer treated with whole-brain radiotherapy (WBRT) with or without sequential systemic chemotherapy. Patients and Methods: All patients were required to have an initial KPS of at least 70%. During the first six months, the patients were re-examined every four weeks, later every 3 months or whenever the clinical condition worsened. Due to slow accrual, the protocol was closed prematurely in 2005. Sixteen adult patients (median age 56 years) treated with 10x3 Gy were studied. Results: Late adverse events \(\geq\) grade 2 (CTC AE v3.0) in imaging-confirmed absence of progressive brain metastases developed in 3 patients after a median of 5 months. With a median overall survival of 7 months, the actuarial risk of late adverse events at that time was 0% after WBRT alone and 37% after WBRT and chemotherapy. Thus, larger studies assessing the impact of multimodal treatment are recommended.

Patients with brain metastases from non-small cell lung cancer (NSCLC) often present with generally advanced spread, \textit{i.e.} multiple rather than solitary brain metastases, and extracranial metastases (1-7). Therefore, the treatment of many of these patients includes palliative whole-brain radiotherapy (WBRT). Besides temporary hair loss, only a few acute side-effects result from WBRT (8). However, a certain proportion of patients might be at risk for development of late neurological adverse events with more serious consequences for their quality of life. After initial retrospective studies (9, 10), we attempted to evaluate these aspects of WBRT prospectively in a selected cohort of adults with at least 2 brain metastases from NSCLC and anticipated survival of more than 3-4 months.

Patients and Methods

Inclusion criteria were chosen on the basis of previous analyses of prognostic factors, such as class, on recursive partitioning analysis (RPA) (11). All patients were required to have a Karnofsky performance status of at least 70% (\textit{i.e.} RPA class I or II), absence of hepatic metastases, age up to 75 years, histologically verified NSCLC, imaging evidence of brain metastases (previously untreated), and had to provide informed consent. Based on previous reports on confounding variables (10, 12), patients on anticonvulsant, neuroleptic or antidepressant medication were excluded. The use of dexamethasone was allowed as indicated to control edema and symptoms of increased intracranial pressure. However, rapid dose reduction and discontinuation was encouraged.

The patient characteristics are shown in Table I. WBRT was administered via standard lateral opposed 6 MV beams from a linear accelerator with 10 fractions of 3 Gy and use of a thermoplastic mask fixation of the head. The dose was prescribed to the midline. Systemic chemotherapy was to be given as indicated for extracranial disease, but not simultaneously with WBRT. A baseline clinical examination was performed within 2 weeks before the start of WBRT. For the first six months after WBRT, the examination was repeated every 4 weeks. Thereafter, follow-up took place at intervals of 3 months. All patients were instructed to come back immediately for re-evaluation if any clinical deterioration should develop. At each examination, the neurological status, orientation, vigilance, mental state and KPS were recorded, according to a pre-defined protocol, by the same physician. In addition, the spouses were asked to provide their judgement of side-effects and daily activities. Computed
**Table I. Overview of patient characteristics.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; median, range)</td>
<td>56, 45-75</td>
</tr>
<tr>
<td>Karnofsky performance status (median, range)</td>
<td>80%, 70%-90%</td>
</tr>
<tr>
<td>Extracranial metastases</td>
<td>7/16</td>
</tr>
<tr>
<td>Uncontrolled primary tumor</td>
<td>8/16</td>
</tr>
<tr>
<td>RPA class I vs. II</td>
<td>4 vs. 12</td>
</tr>
<tr>
<td>Female vs. male gender</td>
<td>6 vs. 10</td>
</tr>
<tr>
<td>No chemotherapy*</td>
<td>5/16</td>
</tr>
<tr>
<td>Chemotherapy only after WBRT</td>
<td>9/16</td>
</tr>
<tr>
<td>Chemotherapy before and after WBRT</td>
<td>2/16</td>
</tr>
</tbody>
</table>

WBRT: whole-brain radiotherapy; *defined as 2 weeks before WBRT, during and after WBRT.

tomography or magnetic resonance imaging of the brain were performed every 3 months. When clinical symptoms worsened, imaging was mandatory to obtain a differential diagnosis between progression of brain metastases and side-effects. In addition, blood counts and chemistry were taken in order to exclude, for example, anemia as a potential reason for decreased performance.

An end-point of ≥ grade 2 adverse events was chosen because grade 1 symptoms can be both difficult to detect without comprehensive test batteries and difficult to interpret regarding their underlying causes in the context of multimodal cancer treatment for metastatic NSCLC. Furthermore, grade 1 symptoms do not cause relevant limitations of independent functioning. Expected accrual was 15 patients per year for a total of 45 patients in 3 years. Actuarial analyses of survival and toxicity-free survival were performed according to the method of Kaplan and Meier (13).

**Results**

Overall, 16 patients were included during 2004 and 2005. Due to this very slow accrual, the study was closed prematurely. The follow-up of the two patients alive at the time of data analysis was just over one year each. All patients had completed their prescribed course of WBRT and none had progression of brain metastases within the first 3 months. Thereafter, 7 patients developed evidence of progression on imaging studies. In case of salvage treatment, such as radiosurgery, patients were taken off the study. No remarkable acute side-effects occurred. Median overall survival from the start of WBRT was 7 months. Systemic treatment was variable, but typically included a platinum compound, taxane, gemcitabine or vinorelbine in the form of a 2-drug combination. Late neurological adverse events were scored according to the Common Terminology Criteria for Adverse Events v3.0 (14). A total of 3 patients developed grade 2 or 3 events in the absence of brain metastases progression after a median of 5 months. No higher grades of toxicity were found. The symptoms (Table II) did not respond to treatment with dexamethasone. Their severity remained unchanged during the remaining life-span in two patients. The third patient showed increasing deficits before he died from systemic tumor progression. Two of these 3 patients had received chemotherapy in addition to WBRT. With a median overall survival of 7 months, the actuarial risk of late adverse events at that time was 0% after WBRT alone and 37% after WBRT and chemotherapy.

**Discussion**

Frequent assessment of long-term neurological adverse events in a narrowly defined population of patients with brain metastases from NSCLC and relatively favourable survival expectation appeared feasible, but much more difficult than anticipated with regard to accrual. However, evaluation of truly treatment-related symptoms requires exclusion of the patients with potentially confounding factors, including those using certain drugs (10, 12). We decided not to use a comprehensive battery of neurocognitive and psychiatric tests, whose results might be influenced by learning effects, but to focus on types of toxicity that are bothersome to the patients and their families in their daily lives and which cause a drop in KPS. In each case, other potential causes of deterioration, particularly progression of brain metastases, were excluded. Overall, the risk of brain metastasis progression after administration of 30 Gy was much higher than that of ≥ grade 2 late effects, suggesting the need to develop more effective treatment approaches.

Although reasonable statistical evaluations were precluded by the small number of patients, it appears that patients requiring both WBRT and systemic chemotherapy might have a higher risk of neurological toxicity. Previous studies of combined treatment have not provided detailed analyses of this end-point (3, 6, 15-18). However, they do suggest that though extracranial failure remains the biggest problem, additional chemotherapy prolongs survival (18). With more complex evaluation tools, other groups demonstrated that lung cancer patients showed neuropsychological test results already significantly below average after chemotherapy but that their status did not decline further after WBRT (19). Fewer cycles of chemotherapy were associated with fewer deficits in this population. It has also been suggested that pretreatment neurocognitive impairment can more often be found in patients with large tumor volume and that WBRT provides more benefit than harm to patients with brain metastases, because it improves rather than deteriorates memory, executive and neurological function (20).

Even if significant treatment-related neurological deterioration is uncommon during the limited life-span of most patients with brain metastases, it is unfortunate that
occasional cases do occur and that attempts to ameliorate or reverse the deficits are rarely successful (21). Some of the mechanisms by which radiotherapy might impair neurogenesis and brain function are now better understood than in earlier decades (22). Striking similarities with regard to the death of several putative target cells (various progenitor cells and oligodendrocytes) in the brain were recently found in the first systematic evaluation of three cytotoxic drugs, namely cisplatin, carmustine and cytarabine, in vitro and in vivo (23). Ongoing research hopefully will further elucidate the influence of all the different components of multimodal therapy on brain function and eventually lead to neuroprotective strategies (24).

References


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