Whole-brain radiotherapy for NSCLC patients with multiple brain metastases – an update

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Introduction

Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancers, with the majority of patients having advanced disease at presentation. Between 10-20% present with brain metastases (BM) and up to 40% of patients will develop BM. The overall median survival is reported to average three to four months if treated with whole brain radiotherapy (WBRT) alone.

Management of BM patients conventionally involved steroids to reduce brain oedema, and WBRT alone for patients with multiple BM or combined with surgery or stereotactic radiosurgery (SRS) for oligo BM, followed by systemic chemotherapy for patients with good performance status.

The progress made in radiotherapy techniques and the introduction of tyrosine kinase inhibitors (TKIs) targeted against oncogenic drivers such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK)-rearranged NSCLC have prompted us to re-evaluate the current management strategies for NSCLC patients with multiple BM.

NSCLC and BM – a heterogeneous group

Historically, determining the prognosis of patients with BM has utilised various prognostic indexes including recursive partitioning analysis (RPA), basic score for brain metastases, and graded prognostic assessment (table 1). However, the landscape for NSCLC is evolving rapidly and nowadays it is recognised as a heterogeneous group of patients with various histological subtypes and genomic alterations of varying prognoses that are treated differently based on these findings. Currently, patients with advanced adenocarcinoma are treated with pemetrexed doublets whereas patients with squamous histology are treated with gemcitabine-based chemotherapy. In addition, the introduction of oral TKIs to treat oncogenic-addicted tumours such as EGFR mutations or ALK-rearranged NSCLC have significantly improved median survival compared to the ‘wild-type’ population.

Many of these TKI agents cross the blood-brain barrier in sufficient concentration to exert anti-tumour activity alone without the need for WBRT. Therefore current prognostic indexes, which were based on several solid cancers (including lung, breast, melanoma, colorectal, renal and others) and those from the previous era when genomic information was not available, are no longer accurate to predict the prognosis of NSCLC patients with BM.

From a clinical viewpoint of management of NSCLC patients with BM, we found it useful to classify patients in terms of whether they either have:

1. oncogenic-addicted EGFR or ALK mutation positive NSCLC, or
2. wild-type NSCLC with oligo or multiple BM.

EGFR mutant patients with brain metastases

EGFR mutations are most commonly seen in patients who are of east Asian origin (50% compared to 10% of non-Asians), female and non-smokers. BM are frequent in advanced EGFR-mutated NSCLC, with a reported incidence of 25% present at initial diagnosis and more than 45% of patients developing BM by three years of survival. For these EGFR mutation positive patients with BM, TKIs play an important role in their management. Several phase 2 studies have demonstrated TKI alone can induce response rates of up to 83%, progression-free survival (PFS) beyond six months and overall survival (OS) exceeding 15 months. This approach has the advantage of treating the primary lung disease, extra-cranial metastases and BM concurrently and deferring WBRT for the future, reducing toxicity problems associated with it.

The relative benefits of TKI alone versus WBRT, or whether it is best to give TKI and WBRT concurrently or sequentially, remain unclear and future trials are needed to address these questions. However, based on published studies it is reasonable to use TKI monotherapy first and hold WBRT in reserve for resistant BM or following disease progression after TKI treatment.

ALK mutant patients with brain metastases

ALK mutations are seen in about 4% of NSCLC and are most commonly seen in younger patients who have a minimal or non-smoking history with adenocarcinoma histology. The natural history of ALK-rearranged NSCLC and patterns of spread to the brain is less well understood but, based on retrospective analysis of available data, BM in ALK-rearranged NSCLC are seen in approximately 25% of patients at presentation and in nearly 60% of patients within three years post-diagnosis, similar to that seen for EGFR tumours.

Similar to EGFR-mutated tumours, ALK inhibitor treatment alone has been demonstrated to be active against BM in patients with ALK-rearranged NSCLC. With crizotinib, the first generation ALK inhibitor, over 50% of patients showed BM control at three months and the mean time to disease progression was seven months. For patients who become crizotinib-resistant, the central nervous system is a very common site of disease progression, occurring in up to 70% of patients. Interestingly, many of these relapsed BM appear to respond to the second generation ALK inhibitors, including LDK378 and AP26113. Similar to EGFR-TKI treatment strategy, it is reasonable to use ALK inhibitors up-front first and hold WBRT in reserve for resistant BM, or following disease progression.
after first and second generation ALK inhibitors. The relative benefits of ALK inhibitor alone versus WBRT, or whether it is best to give ALK inhibitor and WBRT concurrently or sequentially, remains unclear and will be need to be addressed by future trials.

**Wild-type NSCLC patients with brain metastases**

In contrast to EGFR mutation or ALK positive tumours, prognosis of wild-type NSCLC with multiple BM remains very poor with WBRT, as recently demonstrated by our TACTIC study.\(^{11}\) In the study involving 80 patients and where the frequency of EGFR mutation tumours was very low, the neurological PFS was only 1.6 months and OS was 2.9 months for patients treated with WBRT alone, despite selecting only patients with age-modified Radiation Therapy Oncology Group (RTOG) RPA class 1 and 2, which predicts a median survival of 7.1 and 4.2 months, respectively. We found the addition of erlotinib with WBRT and as maintenance offered no advantage over WBRT alone.

Currently for BM patients with oligo metastases who are of good performance status, more aggressive local treatment in the form of surgical resection or SRS should be considered as this can improve survival. Adjuvant WBRT following surgical resection or SRS has been shown to reduce two-year intracranial relapse but, as it does not improve survival and is associated with neuro-cognitive deterioration, it should not be recommended to patients to prevent brain metastases.\(^ {14} \) For advanced BM patients with good performance status, it is reasonable to offer WBRT before considering chemotherapy to control the extra-cranial systemic disease. The role of WBRT for poor performance NSCLC patients with BM is unclear. The QUARTZ study is examining the role of steroids with or without WBRT in patients for whom the clinical benefit of WBRT is less certain.\(^ 9 \)

**Whole brain radiotherapy**

The aim of WBRT is to alleviate symptoms and gain local cranial control. Traditionally, the whole brain is treated to ensure micro-metastatic disease elsewhere within the brain is encompassed within the treatment field. In the UK, 20Gy in five fractions treatment schedule is frequently used but, various doses and schedules of radiation have been employed, including 30Gy in 10 fractions which is popular in the US. Randomised trials and systemic review for radiation doses ranging from 10Gy in one fraction to 54.4Gy in 34 fractions given twice a day over 17 days have shown that no one schedule is superior in achieving disease control or survival advantage\(^ {11} \) (table 2).

WBRT is not without its side effects and patients commonly experience lethargy and somnolence during and in the period of treatment, as well as temporary hair loss, exacerbations in neurological symptoms, headaches, nausea and vomiting. Long term side effects include potential neurocognitive decline and memory loss with a clinically significant reduction in mini-mental state examination being seen in 30-40% of patients at 18 months.\(^ {15} \)

Although the effect of WBRT on neurocognitive function may not be clinically relevant currently for BM patients with wild-type tumours because of shortened survival, improving and improving strategies have improved response rates, such as immunotherapy with anti-PD1 and anti-PDL1 and maintenance strategy, mean we cannot ignore the neurocognitive risks and complications associated with WBRT treatment for these patients who may survive 'long term'.

**Hippocampal sparing**

The hippocampus and limbic system are important in memory function and there has been increasing interest in examining hippocampal sparing brain radiotherapy techniques in order to reduce neurocognitive deterioration. Currently, there are still a number of controversies regarding the role of hippocampal-sparing brain radiotherapy, including the lack of level 1 evidence recommending clear dose constraints, the feasibility of achieving these dose constraints without compromising dose to target volume, and perhaps more importantly, whether it will translate to meaningful clinical results.

It has been suggested from a recent phase 2 trial that the radiotherapy dose to the hippocampus should be low for patients when it is expected their survival will exceed six months.\(^ {26} \) In order to achieve this, intensity modulated radiotherapy (IMRT) and or volumetric modulated are radiotherapy (VMAT) techniques are required. This technology is time consuming, expensive and needs to be balanced against the probability of long survival and improved quality of life.\(^ {25} \) Only randomised trials can evaluate whether these approaches reduce long-term neurocognitive complication and are cost-effective when compared to WBRT. Patients with EGFR mutation or ALK-positive NSCLC who have progressive intracranial disease following TKI therapy and are now being considered for WBRT are the most likely cohorts that may benefit most from this approach. Patients who have only one BM treated with SRS or surgical resection may also benefit from hippocampal-sparing WBRT immediately following their treatment, and the recently opened UK HIPPO trial (hippocampal sparing whole brain radiotherapy versus conventional whole brain radiotherapy in patients with brain metastases) aims to answer this question.

**Conclusion**

Best practice for management of patients with NSCLC with multiple BM has changed following the introduction of TKIs to treat oncogenic-addicted tumours. The incidence of BM is likely to increase in the future as a result of new and improved local and systemic treatment modalities.

For patients with good performance status and oligo BM, one should consider surgery or SRS. Patients with EGFR sensitising mutations or ALK rearranged tumours can potentially be treated with targeted agents alone. There are increasing reports indicating that BM in such patients can be well controlled with TKI alone, avoiding the need for immediate WBRT. For resistant BM or if progressive multiple BM develop after TKI treatment, then WBRT can be given after, with consideration for a possible hippocampal sparing technique if available. Such a strategy limits the acute and long-term toxicities including somnolence and neurocognitive deficit associated with WBRT.

Trials are now needed to examine the role of WBRT in oncogenic-addicted NSCLC. In addition, a new prognostic index needs to be established for NSCLC patients developing BM, which needs to take into consideration the molecular alteration and histology which are now used to customise treatment.

**References**

Pooled data shows no statistically significant difference in overall survival at six months compared to 30Gy in 10#.

Table 1
Factors encompassed in prognostic indexes used for patients with brain metastases. Reproduced from Owen and Souhami 2014.1

<table>
<thead>
<tr>
<th>Regime</th>
<th>Study</th>
<th>Comparative findings</th>
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<tr>
<td>10Gy in 1#</td>
<td>Harwood et al16</td>
<td>Pooled data shows no significant difference in overall mortality at six months compared to 30Gy in 10#</td>
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<tr>
<td>12Gy in 2#</td>
<td>Priestman et al19</td>
<td>Direct comparison between the two most commonly used regimes of 20Gy in 5# and 30Gy in 10# showed no significant difference in overall survival</td>
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<tr>
<td>20Gy in 5#</td>
<td>Chatani et al20, Borgelt et al21</td>
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<td>30Gy in 10#</td>
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<tr>
<td>40Gy in 20#</td>
<td>Borgelt et al21</td>
<td>Pooled data shows no statistically significant difference in overall mortality at six months compared to 30Gy in 10#</td>
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<tr>
<td>50Gy in 20#</td>
<td>Chatani et al22, Kurtz et al23</td>
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<tr>
<td>54.4Gy in 34# BD/ 17d</td>
<td>Murray et al24</td>
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Table 2
Table summarising studies investigating various WBRT regimes for BM. # – fractions; BD – twice a day; d – days. No difference in symptom control detected across trials that reported on symptoms. No statistically significant difference in improvement in neurological function was found on meta-analysis.17