Tyrosine Kinase Inhibitors in the Treatment of Choroidal Metastases from Non-Small-Cell Lung Cancer: A Case Report and Review of Literature

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NSCLC, especially those in which an EGFR mutation is noted. Even in the absence of such mutations, choroidal metastases may show a favorable effect in response to TKIs, such as erlotinib.

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Case Report

A 78-year-old male patient presented with a 3-month history of gradually progressive diminution of vision in the left eye. He had no associated complaints of redness, watering, pain, or discharge. On ocular examination, best corrected visual acuity in the right eye was 20/25, N6 and 20/60, N10 in the left eye. Anterior segment evaluation was unremarkable in both eyes except for pseudophakia. Intraocular pressure in both eyes was normal. Dilated fundus evaluation of the right eye was normal. The left eye however showed a well-defined yellowish-colored circular subretinal lesion along the superior arcade (fig. 1a). The mass had feathery margins and measured approximately two disc diameters in size. The vitreous cavity was clear with no signs of inflammation. Small, discrete, pinpoint yellowish ‘satellite lesions’ were also noted between the optic disc and the macula. In the early phase, fluorescein angiography showed central hypofluorescence with a ring of peripheral hyperfluorescence that gradually increased in intensity and size in the late phase (fig. 2). Optical coherence tomography (OCT) of the left eye through the macula showed neurosensory detachment with the presence of subretinal fluid (fig. 3a). Scans through the lesion showed an irregular, dome-shaped subretinal lesion (fig. 4a). The retinochoroidal junction was indistinct and the underlying choroid had assumed an uneven, hump-shaped configuration. Choroiditis, choroidal granuloma, and choroidal metastasis were the differential diagnoses that were considered. Hematological investigations revealed no infective disease pathology, and an exhaustive panel of serological investigations gave no results suggestive of any autoimmune disease process. Apart from a long-standing history of systemic hypertension and ischemic heart disease, the patient had no other systemic complaints.

A 7-day course of oral prednisolone at a dose of 1 mg/kg showed no change in the size of the lesion or in vision. At this point, with a working diagnosis of choroidal metastases arising from an occult primary, computed tomography–positron emission tomography (CT-PET) was performed, which showed a metabolically active lesion in the right hilar region measuring 3.5 × 3.0 cm, metabolically active mediastinal and tracheobronchial lymph nodes, and multiple lesions in the vertebrae. The findings corroborated the CT images, which showed a possible primary lesion to be a mass arising...
in the right lung along with lytic bony lesions. A CT-guided biopsy was performed and on examination, it was found to be an adenocarcinoma with papillary configuration (fig. 5). Therefore, a final diagnosis of American Joint Committee on Cancer stage IV (T2a N2 M1b) papillary adenocarcinoma of the lung with choroidal and bone metastases was arrived at. As per standard protocol, the tumor cells were tested (TaqMan probe-based endpoint genotyping mutation analysis by real-time polymerase chain reaction on the LightCycler 480 II; Roche Diagnostics, Risch-Rotkreuz, Switzerland) to detect EGFR mutations. No mutations were found on exons 18, 19, 20, and 21, therefore the EGFR was classified as ‘wild-type’.

Palliative chemotherapy consisting of cisplatin and docetaxel was advised, with the option of palliative radiation also being discussed. However, the patient declined any form of intravenous chemotherapy or radiation. He was therefore prescribed oral erlotinib, 150 mg daily. At 6-month follow-up the size of the choroidal tumor had decreased (fig. 1b), and OCT showed dramatic resolution of the choroidal mass with resorption of subretinal fluid (fig. 3b, 4b). The patient’s vision had improved to 20/25 in the left eye. At the last follow-up at 1 year, PET scans showed a good response at other sites of metastases; the patient was on oral erlotinib and had no new metastatic lesions or recurrence of the choroidal lesion.

**Discussion**

The treatment of choroidal metastases depends on many factors such as systemic status, laterality, presence of subretinal fluid, size, and number of tumors [5]. Tak-
ing all factors into consideration, our patient was advised to undergo palliative radiation and systemic chemotherapy consisting of platinum doublets. However refused radiation and any form of intravenous medications. He was then counselled further and prescribed oral erlotinib 150 mg. Erlotinib, a TKI, received FDA approval in cases of NSCLC as first-line treatment for patients with an EGFR mutation and as second-line treatment in advanced NSCLC if there is a relapse or disease progression after the first-line platinum-based combination treatment [5].

The EGFR protein itself is a transmembrane glycoprotein consisting of an extracellular ligand-binding domain, a transmembrane domain as well as an intracellular tyrosine kinase domain [6]. EGFR plays an important role in cancer cell proliferation, angiogenic growth factor production, and cancer cell invasion [7]. Some NSCLCs express EGFR and many tumors have EGFR mutations or gene amplifications. In patients in whom tumor cells have EGFR mutations, the growth of the tumor cells is nearly completely dependent on this EGFR signaling pathway. Hence, any disruption of this pathway causes regression of the tumor [8]. TKIs bind to the intracellular tyrosine kinase catalytic domain and block receptor autophosphorylation and downstream the signal. This leads to a cascade of events that finally lead to tumor growth arrest [9]. Therefore, the presence of these mutations indicates high sensitivity to a group of drugs known as TKIs. The advantage of such targeted therapy over conventional chemotherapy is more specificity towards tumor cells, a broader therapeutic window, and significantly less toxicity. Erlotinib has a relatively good safety profile, with only dose-dependent reversible side effects such as diarrhea and acneiform rashes [7].

Prior to the commencement of TKI therapy, it is required to screen for EGFR mutation in all NSCLCs on immunohistochemistry, fluorescence in situ hybridization, or mutational analysis [10]. The presence of EGFR mutations in adenocarcinoma is a predictor of responsiveness of the tumor to EGFR-TKIs [11, 12]. The most commonly detected mutations are deletions in exon 19, point mutation in exon 21 or insertions in exon 20. Cases that are mutation-negative are designated as ‘wild-type’ NSCLC [12].

There have been few reports documenting the response of choroidal metastases to erlotinib (table 1) [5, 7, 8, 13–17]. However, of the cases reported in the literature, only in three reports were the patients actually screened for genetic anomalies related to EGFR [7, 15, 17]. Of those, 2 patients were found to have aberrations with exon 19 and 1 with exon 21. None of the previously reported cases were found to have no mutation, i.e. to be ‘wild-type’. Among the TKIs, erlotinib was used more often than gefitinib. Most cases showed resolution of the choroidal tumor upon initiation of oral TKI therapy. However, 2 cases stand out. The first report is by Chen et al. [7], who reported the case of a 68-year-old female with metastatic papillary carcinoma of the lung with choroidal metastasis. Testing for EGFR mutations revealed a mutation at L861Q on exon 21. Oral erlotinib provoked a dramatic response with an improvement in tumor size and vision. However, after 7 months of treatment the choroidal lesion had increased in size, and subretinal fluid was noted which caused a drop in vision, necessitating a change in the treatment regimen [7]. The other case of interest is a 73-year-old male whose metastatic NSCLC was treated with systemic chemotherapy that included oral erlotinib [16]. The choroidal lesions worsened while he was on oral erlotinib, following which the lesions showed improvement on treatment with intravitreal bevacizumab; they remained stable for 4 months. No details on EGFR mutation screening are available for the second case. While EGFR mutations usually indicate a possible beneficial response to TKIs, here we have two different cases: one with an EGFR mutation that initially improved and then worsened, and the other, presumed to be wild-type, showing no beneficial response to erlotinib. Our case is different from both as despite having no detectable mutation, i.e. being wild-type, a dramatic response in tumor size was noted. This throws up more questions: Is there more to TKIs than merely EGFR blockage? Are there other factors at play [18]?

It is generally accepted that even in wild-type NSCLCs, TKIs – when used as second line drugs – demonstrate similar response rates, progression-free survivals, and median overall survivals as conventional chemotherapy agents [19–21]. While there is evidence to back the treatment of mutation-positive NSCLCs with TKIs as first-line therapy [22], conventional chemotherapy has been reported to be more effective than TKIs in mutation-negative patients [23]. First-line chemotherapy for NSCLC is usually cisplatin-based and can have significant adverse reactions. Conventional chemotherapy interferes with cell division and does not discriminate sufficiently between rapidly dividing tumor cells and normally dividing noncancerous cells. Therefore, toxic adverse effects like bone marrow suppression, nephrotoxicity, and hepatotoxicity are common. In comparison to this, targeted biologic agents like TKIs aim at disrupting specific molecular pathways that are involved in tumor growth, prolifera-
tion, and metastasis, thereby causing minimal collateral damage [7]. Therefore, in advanced cases of NSCLCs with systemic metastases, where chemotherapy may worsen the quality of 'life near death', therapy with oral TKIs may be considered in cases of choroidal metastases from NSCLCs [24].

We believe our case demonstrates that newer drugs like erlotinib can be useful in the treatment of choroidal metastases in cases of NSCLC that overexpress EGFR. The use of TKIs to treat choroidal metastases from the lung may be considered even in the absence of any detectable mutations.

### Table 1. Summary of the cases of choroidal metastases from NSCLC in the literature treated with EGFR-TKIs

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/sex</th>
<th>Lung cancer subtype</th>
<th>Initial vision</th>
<th>Other sites of metastases</th>
<th>EGFR status</th>
<th>Other concurrent chemotherapy</th>
<th>EGFR-TKI used</th>
<th>Other intravascular treatment for choroidal metastasis</th>
<th>Outcome</th>
<th>Final vision after treatment with EGFR-TKI</th>
<th>FU period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al. [13], 2009</td>
<td>57/F</td>
<td>NSCLC – adenocarcinoma</td>
<td>20/200</td>
<td>yes; sites NS</td>
<td>NS</td>
<td>yes; docetaxel + cisplatin</td>
<td>erlotinib</td>
<td>intravitreal bevacizumab</td>
<td>resolution of choroidal lesion</td>
<td>20/40</td>
<td>4 months</td>
</tr>
<tr>
<td>Daniels et al. [8], 2010</td>
<td>43/M</td>
<td>NSCLC – adenocarcinoma</td>
<td>HM</td>
<td>yes; bone, brain</td>
<td>NS</td>
<td>yes; carboplatin + paclitaxel</td>
<td>erlotinib</td>
<td>no</td>
<td>resolution of choroidal lesion</td>
<td>20/25</td>
<td>3 years</td>
</tr>
<tr>
<td>Inoue et al. [14], 2010</td>
<td>68/F</td>
<td>NSCLC – adenocarcinoma</td>
<td>20/200</td>
<td>NS</td>
<td>NS</td>
<td>no</td>
<td>gefitinib</td>
<td>no</td>
<td>resolution of choroidal lesion, subretinal fluid reduced</td>
<td>20/100</td>
<td>3 months</td>
</tr>
<tr>
<td>Shimomura et al. [15], 2013</td>
<td>53/F</td>
<td>NSCLC – adenocarcinoma</td>
<td>20/200</td>
<td>yes; bones, malignant pleural effusion</td>
<td>exon 19 deletion mutation (delE746-A750)</td>
<td>no</td>
<td>gefitinib</td>
<td>no</td>
<td>resolution of choroidal lesion, subretinal fluid reduced</td>
<td>20/100</td>
<td>5 months</td>
</tr>
<tr>
<td>Chen et al. [7], 2011</td>
<td>68/F</td>
<td>NSCLC – papillary carcinoma</td>
<td>20/60</td>
<td>yes; thyroid, lung, bones</td>
<td>exon 21 mutation (L861Q)</td>
<td>no</td>
<td>erlotinib</td>
<td>no</td>
<td>initial improvement followed by worsening</td>
<td>20/25b</td>
<td>7 months</td>
</tr>
<tr>
<td>Lai et al. [16], 2012</td>
<td>73/M</td>
<td>NSCLC – adenocarcinoma</td>
<td>20/200</td>
<td>yes; sites NS</td>
<td>NS</td>
<td>yes; vinorelbine + cisplatin</td>
<td>intravitreal bevacizumab</td>
<td>no</td>
<td>worsened</td>
<td>10/200</td>
<td>2 monthsc</td>
</tr>
<tr>
<td>Fujiu et al. [17], 2012d</td>
<td>49/M</td>
<td>NSCLC – adenocarcinoma</td>
<td>20/200</td>
<td>NSd</td>
<td>exon 19</td>
<td>NSd</td>
<td>erlotinib</td>
<td>no</td>
<td>resolution of choroidal lesion</td>
<td>20/18</td>
<td>4 daysd</td>
</tr>
<tr>
<td>Ye et al. [5], 2014</td>
<td>48/F</td>
<td>NSCLC – subtype NS</td>
<td>20/100</td>
<td>yes; bone, brain</td>
<td>NS</td>
<td>no</td>
<td>erlotinib</td>
<td>no</td>
<td>resolution of choroidal lesion</td>
<td>20/25</td>
<td>5 months</td>
</tr>
<tr>
<td>Current case</td>
<td>78/M</td>
<td>NSCLC – adenocarcinoma</td>
<td>20/60</td>
<td>yes; bones</td>
<td>wild-type</td>
<td>no</td>
<td>erlotinib</td>
<td>no</td>
<td>resolution of choroidal lesion</td>
<td>20/30</td>
<td>1 year</td>
</tr>
</tbody>
</table>

Singh et al. [25] in their series reported two cases of lung cancer with choroidal metastases that received EGFR-TKIs. EGFR mutation status was not specified for either patient. One patient received oral gefitinib as second-line chemotherapy and the other oral erlotinib as third-line palliative medication. None of the cases had an ophthalmologic follow-up documenting the disease after initiation of TKI, hence they were not included in this table. FU = Follow-up; HM = hand movement; NS = not specified.

a Choroidal lesions responded to gefitinib, but the patient developed brain metastases while on gefitinib, hence it was discontinued. b After 7 months, reaccumulation of subretinal fluid was noted and vision dropped to 20/80, which prompted a change of drug to docetaxel. c The choroidal lesions worsened while the patient was on oral erlotinib, following which they showed improvement on treatment with intravitreal bevacizumab, remaining stable for 4 months. d The details of this case are from the English abstract (the original article is in Japanese).
Disclosure Statement

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interest, and expert testimony or patent licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs), in the subject matter or materials discussed in this paper.

Statement of Ethics

This submission complies with the guidelines for human studies and animal welfare regulations. This paper does not involve any experimental drug that does not have FDA approval. The treatment of the subject described in this paper was carried out after obtaining informed consent. No animal experiments were carried out with regards to this submission.

References

4 Ferry AP, Font RL: Carcinoma metastatic to the subject matter or materials discussed in this paper.

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