To the Editor: The incidence of intraocular metastases is approximately 8% to 10%,[1] of which choroidal metastasis (CM) is the most painful metastatic lesion. CM is a growing problem in the context of an aging population and improved survival among stage IV cancer patients. Lung cancer is the second most common primary malignancy associated with CM. Clinical symptoms vary greatly depending on the location of the lesion or the degree of invasion. Acute clinical symptoms will significantly impair quality of life among surviving patients. The main therapeutic modalities include systemic and local treatments, while observation is also a treatment option. Currently, the feasibility and effectiveness of various treatment options are controversial around the world. Given the rarity of this condition, it is almost impossible to conduct large-scale clinical trials to validate optimal treatment modalities, rather, clues and insights may derive from a series of small trials to validate optimal treatment modalities, rather, clues and insights may derive from a series of small sample reports. Herein, we reviewed the related literature from 2009 to 2019, from which relevant information was extracted to elucidate the epidemiological and clinical characteristics of CM and to provide suggestions for the treatment of this condition.

This retrospective review included 57 cases of CM from lung cancer reported in the English literature. Reports were identified by searching PubMed (National Library of Medicine, Bethesda, MD, USA) for articles published from 2009 to 2019. Publications describing ocular involvement other than the choroid were excluded, as were publications that were not in English, those not reporting data on individual patients, or those without available full-text. Demographic characteristics and the survival details of all patients are presented in Supplementary Table 1, http://links.lww.com/CM9/B63.

SPSS 23.0 statistical software (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. Measurement data are presented as mean ± standard deviation and count data are presented as percentages.

Among these 57 cases, the median age was 52.0 ± 13.6 years (range: 25.0–78.0 years). The male-to-female ratio of patients in our study was 0.73:1, with no significant sex predilection. The number of patients who were firstly diagnosed with choroidal metastatic carcinoma, followed by a diagnosis of lung cancer, was 38, accounting for 67% of all cases.

Regarding the ocular involvement, 26% (n = 15) involved both eyes, 30% involved the right eye (n = 17), and 44% involved the left eye (n = 25). Single lesions accounted for 74% (n = 42) of cases, while multiple lesions were identified in 26% (n = 15) of cases. Similar to the series reported by Shah et al,[2] the present data showed that CM derived from lung cancer had a modest left eye predominance and was most often unifocal.

Lung adenocarcinoma was the most common pathological type, accounting for 79% of all cases. The clinical staging was available for approximately 13 patients, most of whom were diagnosed with T2 (n = 8), followed by N2 (n = 7) lesions. Approximately, 86% of patients with intraocular metastases presented other metastasis sites, simultaneously. The most frequently identified mutation type in patients with oncologic driven genes was the anaplastic lymphoma kinase (ALK) fusion gene, accounting for 18%. Additional detailed clinical information is provided in Figure 1A–C.

Regarding treatment options, of the 57 patients, 28 received systemic treatments alone, 20 patients received combined local and systemic treatments, and local...
treatments alone were used in nine patients. The various treatment modalities and their therapeutic results are summarized in Figure 1D.

Small-molecule tyrosine kinase inhibitors (TKIs) were administered to 17 patients, of which 12 patients received first-line treatment (1 patient harbored negative driver gene, yet TKI treatment was still effective), whereas five patients received second-line treatment. In patients treated with newer generation TKIs (alectinib, ceritinib, and osimertinib), intraocular lesions were well controlled, regardless of the treatment used. Furthermore, the probability of concomitant brain metastases was estimated at 16% (9/57) in this study. Newer generation TKIs offer increased central permeability and a favorable local disease control rate (DCR), with a markedly improved progression-free survival for brain metastases. One patient included in this review with concomitant intraocular and intracranial metastases received alectinib and achieved regression at both sites.[3]

Of the 16 patients treated with systemic chemotherapy, 14 patients received first-line treatment. Except for two patients, whose chemotherapy regimen was unspecifed, the remaining 14 patients were treated with platinum-based doublet chemotherapy, including five cases with pemetrexed plus cisplatin (AP) regimen, two cases with paclitaxel plus carboplatin (TC) regimen, one case with gemcitabine plus carboplatin (GC) regimen, and one case with gemcitabine plus cisplatin (GP) regimen. Five patients received intravenous bevacizumab in combination with systemic chemotherapy. The responses of systemic and ocular lesions to chemotherapy were identified in 7 and 16 patients, respectively.

In our data, chemotherapy has been less effective in controlling systemic lesions, while targeted therapy has been shown to have a more favorable outcome both for intraocular metastases (DCR: 82% vs. 79%) and systemic lesions (DCR: 82% vs. 57%).

Intravitreal bevacizumab (IV-Bev) was administrated in combination with systemic therapies in nine patients. The number of IV-Bev doses administered ranged from 1 to 7 (average: 3.50 doses) per patient, with each administration consisting of 1.25 or 2.50 mg. There is no standard dose for the treatment of intraocular metastases. In most cases, the dose chosen ranged from 1.25 to 4.00 mg.[4-6] Two patients included in this review received a targeted agent combined with IV-Bev and intracranial tumors for both patients were significantly reduced in size. IV-Bev combined with systemic therapies demonstrated a well-controlled local DCR of 75%, while the systemic response was poorer than that of systemic therapy.

Ocular radiotherapy combined with systemic therapies was used in 12 patients, of which eight cases identified a specific type of radiotherapy: four cases of external beam radiation therapy (EBRT), two cases of whole-brain radiation encompassing the affected eye, one case of three-dimensional conformal radiation therapy (3D-CRT), and one case of stereotactic body radiation therapy. In addition, one patient underwent plastic eye surgery.
following improvements in response to TKIs. Among those treated with combination systemic regimens, one received erlotinib and 11 patients were treated with systemic chemotherapy. One patient underwent enucleation after radiotherapy due to an inadequate response to ocular symptoms.

Local treatments alone were reported in nine patients, including IV-Bev \((n=3)\), proton beam therapy (PBT, \(n=1\)), a laser with 3D-CRT \((n=1)\), photodynamic therapy (PDT) combined with EBRT \((n=1)\), EBRT \((n=2)\), and total brain radiation that encompasses the affected eye \((n=1)\). The response rate of ocular lesions to local treatment alone was just 43%.

Local treatment alone \((43\%)\) and systemic therapy combined with ocular radiotherapy \((40\%)\) achieved lower DCR than systemic therapy combined with IV-Bev \((75\%)\).

The duration of vision improvement/regression was reported in 43 cases, with a median duration of 10.60 ± 8.31 months \((95\% \text{ confidence interval [95\% CI]: 8.04–13.16 months})\).

Quantification of overall survival (OS) since CM diagnosis was available for 22 cases, with a median OS of 12.14 ± 9.92 months \((95\% \text{ CI: 7.73–16.53 months})\).

By analyzing 57 patients diagnosed with CM from lung cancer, we identified several noteworthy findings that might be helpful to understand and manage this condition. First, we found that 67% of patients complained of ocular symptoms as their initial presentation of lung cancer. These findings suggest that the presence of CM in a patient without known cancer should be differentially diagnosed for the possibility of primary lung cancer. Second, approximately 86% of patients simultaneously present metastases at other sites. Third, according to the data collected in this study, the DCR achieved by targeted therapy for local CM was significantly higher than that by conventional chemotherapy. Newer generation TKIs offer increased central permeability and a favorable local DCR. Therefore, for lung cancer patients harboring sensitive gene mutations and CM, targeted therapy, especially second- or third-generation targeted agents, may be the optimal treatment choice. Local DCR was lowest for systemic therapy plus local radiotherapy \((40\%)\) and local therapy alone \((43\%)\) than for patients treated with systemic therapy alone \((targeted therapy: 82\%; chemotherapy: 79\%)\). These findings may be related to the fact that patients in our collection of cases treated with local radiotherapy, often second line and above, had limited life expectancy and rapid tumor progression. Therefore, it is essential to conduct randomized controlled clinical trials to compare the effects of different treatment modalities head-to-head, when available. Meanwhile local therapies, such as ocular radiotherapy, may be applied with caution to relieve local symptoms, especially when a patient presents with acquired resistance to systemic therapy, while the potential for treatment-related side effects should also be taken into consideration.

In this study, we summarized the clinical case reports in the past 10 years to provide a reference for clinical oncologists in the treatment of such patients. However, due to the limited nature of case reports, there was significant heterogeneity among the clinical characteristics of patients, included in the study and in the individual treatment choices, which can lead to bias and shortcomings in some of the data from this study. Nevertheless, our findings may provide some data supporting subsequent clinical studies.

In summary, CM is relatively common in middle-aged patients with lung adenocarcinoma. The treatment modalities for CM from lung cancer depend on the extent and response of the systemic metastatic disease. For patients with sensitive gene mutations, small molecular TKIs as systemic therapies can induce regression in both systemic and ocular lesions and may be sufficient for temporary relief of visual symptoms. A multimodal team for the treatment of this kind of metastatic disease is necessary to acquire control of both local and systemic diseases. A combination of systemic and local IV-Bev treatments that showed greater tumor regression compared to single treatment alone is recommended. In selected cases, novel radiotherapy techniques that lead to fewer side effects could be taken into consideration. New treatment modalities, such as immunotherapies, require further exploration in the future.

Conflicts of interest

None.

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