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Short Communication

Systemic Therapy Options for Leptomeningeal Carcinomatosis

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DESCRIPTION

Leptomeningeal Carcinomatosis (LMC) is rare yet devastating complication of advanced malignancies whereby cancer cells metastasize to the leptomeninges, namely the arachnoid and the pia mater, causing neurological symptoms *via* cancer involvement of the cerebrospinal fluid. LMC is an incurable condition and confers a very poor prognosis, with median overall survival rate of 2 to 3 months [1]. Common manifestations of LMC include headache, nausea, vomiting, and neck and back pain. Various neurological symptoms have also been reported including facial droop, hallucinations, paresthesia, sensorineural hearing loss, altered mentation, and muscle weakness [2].

Currently, management of LMC is mostly palliative with systemic and/or intrathecal (IT) therapies. However, neither approach is considered sufficiently effective, and although extended survival is occasionally achieved, the goals of treatment remain palliation of symptoms and improving quality of life. Due to relative rarity of this condition (LMC is diagnosed in about 5 percent of patients with advanced cancer) and short average survival period, patients with LMC are frequently excluded from clinical trials, thus limiting systemic evaluation of novel therapies in this population of patients with poor prognosis [3]. Systemic therapy is preferred over IT therapy for most patients with a systemic therapy option that has both efficacy against the primary tumor and a reasonable likelihood of Central Nervous System (CNS) penetration or activity. There are now a number of new systemic therapies across various cancers that have offered more targeted approach and have a higher likelihood of CNS penetration.

In breast cancer, recent approval of an oral Tyrosine Kinase Inhibitor (TKI), tucatinib, was based on the fact that the drug showed an improved overall survival and was especially effective in patients with CNS metastases [4]. The progression-free survival at 1 year for patients with brain metastases (nearly half of the patients on study) was 25% in the tucatinib combination arm, compared to 0% in the placebo combination group (hazard ratio 0.46, P<0.001).

Osimertinib has a significant intracranial activity in patients with Non-Small Cell Lung Cancer (NSCLC). In the phase 1 study, osimertinib, a third-generation oral TKI showed a 41% overall response rate, with median overall survival of 11 months in patients with cytologically confirmed LMC who had previously progressed on EGFR-TKI therapy [5]. In the recent study, adjuvant osimertinib appeared to prevent development of CNS metastases in patients with stage Ib-III NSCLC, with 82% reduction in the risk of CNS recurrence at 24 months, compared to placebo [6].

Similarly, alectinib and other second-generation ALK inhibitors have shown to be effective in treatment of patients with NSCLC and CNS metastases, including LMC. In this study, patients with measurable CNS lesions at baseline had an 81% response with 38% complete response with alectinib, compared to 50%and 1%, respectively, with crizotinib. The duration of response was also longer with alectinib, 17 months *versus* 5.5 months with crizotinib [7].

In patients with BRAF-positive malignant melanoma and brain metastasis at baseline, dabrafenib, a selective BRAF V600E inhibitor, showed a complete or partial response of 30% in a phase II study [8]. Likewise, vemurafenib, another oral BRAF inhibitor, was also effective in treatment of patients with metastatic melanoma and symptomatic CNS involvement, with 37% achieving over 30% response in the brain [9-11].

With these highly active systemic therapies and patients living longer, the incidence of CNS metastases and LMC is expected to be increasing. Understanding the mechanisms of effectiveness (and failure) in the CNS may allow for future development of more effective therapies.

CONCLUSION

Nonetheless, risk of adverse effects must be carefully weighed when choosing these agents. For instance, osimertinib is associated with higher risk of Cancer Therapy-related Cardiac Dysfunction (CTRCD) than conventional EGFR-TKIs. Among ALK inhibitors, alectinib showed an overall improved toxicity profile than crizotinib with less frequent grade 3 to 5 adverse events such as increased liver enzyme levels and QTprolongation. Both BRAF inhibitors dabrafenib and vemurafenib are known to

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cause several dermatologic toxicities including actinic keratosis, hand-foot skin reaction, and cutaneous squamous cell carcinoma. In patients receiving tucatinib, the most common adverse events observed were palmar-plantar erythrodysesthesia syndrome, nausea, vomiting, and fatigue.

REFERENCES

1. Schiff DS, Kesari, Wen PY. "Cancer neurology in clinical practice" in Neurologic Complications of Cancer and Its Treatment. 2008.
2. Chang J, Gao Y, Yu M, Perdomo W, Karki S, Bakirhan K. Colorectal signet ring cell carcinoma with leptomeningeal carcinomatosis: A case report and review of literature. Current Problems in Cancer: Case Reports. 2021;4:100126.
3. Sahebjam S, Forsyth PA, Smalley KS, Tran ND. Experimental treatments for leptomeningeal metastases from solid malignancies. Cancer Control. 2017;24(1):42-46.
4. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382(7):597-609.
5. Yang JC, Kim SW, Kim DW, Lee JS, Cho BC, Ahn JS, et al. Osimertinib in patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer and leptomeningeal metastases: The BLOOM study. J Clin Oncol. 2020;38(6):538-540.
6. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med. 2020;383(18):1711-1723.
7. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib *versus* crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017;377(9):829-838.
8. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): A multicentre, open-label, phase 2 trial. lancet oncol. 2012;13(11):1087-1095.
9. Dummer R, Goldinger SM, Turtschi CP, Eggmann NB, Michielin O, Mitchell L, et al. Vemurafenib in patients with BRAFV600 mutation-positive melanoma with symptomatic brain metastases: Final results of an open-label pilot study. Eur J Cancer. 2014;50(3): 611-621.
10. Kunimasa K, Oka T, Hara S, Yamada N, Oizumi S, Miyashita Y, et al. Osimertinib is associated with reversible and dose-independent cancer therapy-related cardiac dysfunction. Lung Cancer. 2021;153:186-192.
11. Gençler B, Gönül M. Cutaneous side effects of BRAF inhibitors in advanced melanoma: Review of the literature. Dermatology Research and Practice. 2016;2016:5361569.