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Research Article

Incidence of Brain Metastasis in NSCLC Patients in Central India

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Abstract

Introduction: Lung cancer is overall the most common malignancy worldwide and the leading cause of mortality despite the recent advances in its management. Non-small cell lung carcinoma (NSCLC) is the most common histology comprising around eighty percent and adenocarcinoma has recently emerged to be the most common subtype. Ten percent of these patients have brain metastasis at diagnosis and of the rest forty to fifty percent progress to have central nervous system (CNS) disease at some point in their disease course. The advent of targeted therapy and immunotherapy has improved the disease outcome due to their good intracranial activity. Precision oncology has brought a landmark change in the understanding and management of locally advanced NSCLC, the drawback being its high cost making it unaffordable for most patients in our third world country setting. Our study is an attempt to understand and evaluate the incidence of CNS metastasis in non-small cell lung cancer patients in two tertiary care hospitals in central India and its management with limited resources, where majority of our patients are not affordable for most of the molecular studies, targeted and immunotherapy. **Materials and Methods:** CNS metastasis and other clinicopathological markers were retrospectively analyzed in 65 patients diagnosed with NSCLC and treated between 2015-2020. Understanding of disease biology and outcome with basic resources in form of intravenous chemotherapy drugs and locoregional therapies was attempted. **Results:** Adenocarcinoma subtype of NSCLC is rapidly rising in our population; this could be attributed to subclinical tuberculosis (TB) rampant in our part of the world. Brain metastasis was observed in 17% of cases. Despite the unaffordability for precision oncology/ molecular tests, targeted therapy and immunotherapy by our set of patients we observed that standard dose intravenous doublet platinum based chemotherapy along with locoregional treatment in form of radiotherapy, corticosteroids and supportive care had adequate disease control with acceptable quality of life.

Keywords: NSCLC; Adenocarcinoma; CNS Metastasis; BBB Penetration; Tuberculosis; Precision Oncology; Targeted Therapy; Immunotherapy; Radiotherapy.

Introduction

Lung cancer is the most common malignancy in males and females combined with an incidence of 12.4%, and it is also the leading cause of mortality with 1,817,469 cases representing 18.7% of total deaths from this disease [1].

Among these approximately 10% of newly diagnosed patients with advanced non-small cell lung cancer (NSCLC) have brain metastasis. Brain metastasis are the most common intracranial tumors in adults and out of these, lung cancer is the primary site in 40-50% of cases [2-3]. Treatment options for patients with advanced NSCLC and brain metastasis are evolving rapidly and now more than ever the incidence of these metastasis is rising. Factors involved are: first, patients with advanced and metastatic disease are living more years thanks to newer local therapies. Second, incidence of driver mutations specifically epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) are rising, and these patients are more prone to develop brain metastasis. Third, newer targeted therapies against EGRF and ALK

and immunotherapy have great intracranial efficacy which permits the preference of systemic therapies over historically preferred local therapies like WBRT, SRS and SRT in asymptomatic and stable patients leading to increased overall survival [4-6]. One fundamental question is whether this is because patients now are having longer survival rates, thus having more time to develop brain metastasis. Here we present our small series of NSCLC, consisting of 65 cases diagnosed and treated over last 5 years, analysed in retrospective manner providing an overview on CNS metastasis in our patients, including our evolving understanding of molecular landscape, treatment updates and future directions.

Material and Methods

The study was conducted at Ruby Hall Clinic and Galaxy Care Hospital, tertiary care hospitals in Pune. Retrospectively the clinicopathological profile of 65 patients diagnosed with advanced NSCLC was examined and included in this study. Detailed analysis was done and relevant data like histology subtypes, incidence of CNS metastasis, treatment given and outcome of these patients was retrieved.

Results

Out of 65 patients 37 were male and 28 were female, majority were adenocarcinoma 45/65, 18/65 were squamous cell carcinoma and 2/65 were large cell carcinoma.

Clinically or radiologically active TB association was not found in our series of patients and contrary to the belief, most patients (90%) had well preserved normal haemoglobin levels at diagnosis.

All patients were treated uniformly with Platinum based doublet chemotherapy: Pemetrexed and Carboplatin/ Cisplatin for adenocarcinoma patients in first line, while Paclitaxel and Carboplatin was used for squamous cell carcinoma. Other drugs used were Gemcitabine, Docetaxel in second line.

Pemetrexed-Carboplatin combination was extremely well tolerated and gemcitabine was next best tolerated. Docetaxel was difficult to tolerate but had good response in maintaining stable disease and delay progression in second line setting and most patients completed intended cycles with little to no intervention required.

Taxanes were found to be associated with Neurotoxicity in almost all patients: majority (50 patients) had grade 1 toxicity peaking at day 3-5 post chemotherapy, relieved with opiate (narcotic) analgesics and GABA analogues like Tramadol and Pregabalin.

15 patients had grade 2 neurotoxicity leading to drug dose modification in next cycles, out of which 1 female patient had very poor tolerance leading to gait changes and the drug had to be discontinued, she then tolerated Gemcitabine well.

Patients were assessed periodically with serial HRCT scans of chest/ PET scan depending on baseline investigation done or if any suspect of metastatic disease/ disease progression was there or not.

Response assessment criteria was as per RECIST/PERCIST criteria.

10/65 patients developed brain metastasis. The time to brain metastasis varied from at diagnosis (synchronous) to several months after discontinuing the chemotherapy. All these patients having CNS metastasis had proven higher disease grade (grade III and poorly differentiated histology), larger tumor size and burden at presentation. Only two patients had symptomatic CNS disease in form of seizures and personality change as presenting complaints leading to the diagnosis of this advanced form of malignancy on further investigations.

The patients who had limited brain metastasis (1-5 lesions) received locoregional treatment in form of stereotactic radiotherapy/ radiosurgery (SBRT/SRS) along with systemic therapy based on presence or absence of targetable mutation in the molecular profile studies. Eight patients had EGFR positive disease, but none were affordable for Osimertinib based targeted therapy. Most of the patients refused to undergo molecular testing due to financial issues. Few of the patients with brain metastasis could not/ refused radiation to brain and could not receive targeted therapy due to affordability issues, they although continued systemic chemotherapy Pemetrexed Carboplatin in regular therapeutic doses. Although better response was seen with patients receiving local radiation and targeted therapy, some degree of disease stability was also seen with intravenous systemic therapy, to utter surprise they continued to improve in neurological deficit, suggesting crossing over of the BBB in regular doses. Metastatic patients with no targetable mutation were also tested for PD- L1 and 8 patients had positive TPS >1, but none of the patient was affordable for the same hence we could not note the intra-cranial activity of immunotherapeutic agents. Patients with poor general condition and Karnofsky performance status (KPS) less than 70, were offered whole brain radiotherapy (WBRT) and/or best supportive care with corticosteroids and symptomatic management with the aim of providing an adequate quality of life. Adenocarcinoma histology did better than Squamous or other subtypes in our set of patients. This can be attributed to less number of targetable mutations are observed in squamous cell carcinoma, p53 is still the most common mutation in these carcinomas, making it difficult to manage therefore having poorer outcome.

Discussion

The present study was carried out at two tertiary care hospitals in Pune (Maharashtra), retrospectively analysing the clinical records of 65 patients with advanced NCSLC diagnosed and treated between 2015-2020. Data of 65 patients was retrieved and studied, including their histopathological reports. All patients were NSCLC, correlating with findings by Govindan R et al who stated

that NSCLC make up around 80% of all lung cancer patients, out of these around 70% were adenocarcinoma [7]. This rise in incidence of lung adenocarcinoma has risen steadily over the past few decades and as stated by Zhang Y et al, it has become the most common subtype of lung cancer globally [8].

17% patients had brain metastasis at some point in their disease course, which is similar to Ali A et al stating that 20-40% patients with locally advanced disease go on and develop brain metastasis if not already present at diagnosis [9].

In the era of precision oncology, an individualized approach to patient care based on specific molecular alterations is increasingly utilized, nowhere more so than in NSCLC [10].NSCLC is a disease characterized by both intertumoral and intratumor molecular heterogeneity. The molecular analysis of patient with primary lung and brain metastases has implicated several alterations including PI3K/AKT/mTOR, HER2/EGFR and MAPK CDK pathways in driving brain metastases, which may be therapeutically targeted [11].

Currently, there are nine main biomarkers with FDA-approved targeted therapies with varying degrees of CNS activity, including alterations involving multiple EGFR mutations, ALK rearrangement, ROS1 rearrangement, KRAS G12C, BRAF V600E, NTRK1/2/3 fusions, RET rearrangement, and ERBB2 (HER2) [12]. Among patients who develop CNS involvement, specifically, EGFR mutations and ALK rearrangements are particularly common, with an extended survival seen in such patients following the advent of TKIs, therefore allowing more time to develop brain metastases [13]. Our study has several limitations including its retrospective nature, lack of information regarding exact patient staging, knowledge of exact molecular subtype, lack of financially able patients ready to afford costly targeted and immunotherapy. Despite this, adequate and prompt treatment with available resources such as intravenous chemotherapy and radiotherapy along with supportive therapy with corticosteroids and VEGF inhibitors such as Bevacizumab to reduce perilesional brain oedema whenever possible, has led to better symptomatic control/ prognosis and improved overall survival in lung cancer patients in our area.

For future directions, targeting driver mutations of brain metastasis is going to be the next aim. Recently many cases have been observed where the sequencing analysis of metastatic site have demonstrated different alterations as compared to the primary site [14]. Such alterations may be the underlying mechanism conferring the ability to metastasize to the tumor, example being P53 and MYC. Further detailed molecular analysis is needed to understand the genetic microenvironment driving lung cancer brain metastasis with duly effective targeting agents [15-16].

Conclusion

Adenocarcinoma subtype of NSCLC is rapidly rising in our population; this could be attributed to subclinical TB rampant in our part of the world. Brain metastasis was observed in 17% of cases. We postulate that chemotherapy drugs cross BBB in presence of brain metastasis leading to disease control and better quality of life. Despite the fact that many of our patients are positive for targetable mutations such as EGFR, ALK, KRAS and PD-L1, these treatments are not affordable to all. The high cost of precise molecular testing like NGS, liquid biopsy are still out of reach for large proportion of our population. Regardless of the multiple setbacks, systemic chemotherapy, Pemetrexed-platinum based, along with local therapy and adequate supportive care has emerged as a successful way to deal with the burden of advanced NSCLC with CNS metastasis, showing that even our standard intravenous agents have some degree of BBB penetration, leading to disease control and better quality of life in our set of patients.

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