

Carcinomatous meningitis in non-small cell lung cancer: Palliation with intrathecal treatment

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ABSTRACT

Carcinomatous meningitis or meningeal carcinomatosis is seen in up to 5% of patients of metastatic non-small cell lung cancer. However, isolated carcinomatous meningitis without brain parenchymal metastasis is less common. Patients with carcinomatous meningitis have limited treatment options. However, intrathecal therapy if used optimally along with targeted therapy when indicated result in good palliation with improvement in survival.

Key words: *Carcinomatous meningitis, intrathecal chemotherapy, meningeal carcinomatosis*

INTRODUCTION

Carcinomatous meningitis is defined as infiltration of the leptomeninges by malignant cells. With development better chemotherapy and supportive care for management of advanced malignancy more and more patients are surviving longer than before. Longer survival means that more likelihood of disease manifesting in sanctuary sites like central nervous system. Hence, it has become even more pertinent that clinicians develop high index of suspicion for diagnosing patients with carcinomatous meningitis and who present with atypical symptoms.

CASE REPORT

A 51-year-old female patient non-smoker was diagnosed with carcinoma lung in September 2010. Work-up revealed: Staging positron emission tomography computed tomography (PET CT)-Mass lesion in left upper lobe (T1) with N2 lymph node. The biopsy revealed adenocarcinoma. She received 3 cycles of neoadjuvant chemotherapy with pemetrexed and cisplatin. She had near complete

morphologic and metabolic response to chemotherapy on PET CT after 3 cycles of chemotherapy. She underwent left upper lobectomy on 24-12-2010. Histopathology revealed residual foci of adenocarcinoma 0.1 cm (yPT1N0M0). She was on regular follow-up since then. She developed a headache after 16 months of surgery. She presented with headache and occasional vomiting in august 2012. Clinical examination including neurologic examination was normal. Magnetic resonance imaging (MRI) brain revealed extensive leptomeningeal enhancement in the right parietal and occipital lobes though there was no parenchymal metastasis. CT scan thorax and abdomen was normal. Cerebrospinal fluid (CSF) cytology was negative once. Repeat CSF cytology was positive for metastatic carcinoma.

Ommaya reservoir was placed followed by weekly intraventricular methotrexate (MTX) injections. Patient was also started on gefitinib 250 mg once a day. Her tumor sample was analyzed for epidermal growth factor receptor (EGFR) mutation, which was positive. After 3 months of weekly MTX her symptoms improved remarkably. Her headache subsided and vomiting resolved. She received 10-12 mg twice a week for 4 weeks. Consolidation: 10-12 mg every week for 1 month and then every 2 weeks for 1 month. MRI brain repeated at the end of 3 months showed early features of leukoencephalopathy (due to MTX) although the leptomeningeal enhancement resolved completely. Repeat CSF analysis was normal. Hence further doses of intrathecal MTX withheld and she was continued on gefitinib alone. She is asymptomatic after 6 months of relapse.

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DOI:
10.4103/0971-5851.133726

A 71-year-old male patient presented with stage IV lung cancer due to pleural fluid cytology positivity. Initially, started on gefitinib empirically on which he had stable disease for 11 months. However, gefitinib was stopped due to altered liver function test. He progressed after stopping gefitinib hence started on gemcitabine and carboplatin. After six cycles, he had stable disease after which he was started on switch maintenance with pemetrexed. After three cycles of single agent pemetrexed patient developed excessive fatigue.

On clinical examination, he had bilateral ptosis, with normal third nerve function. He underwent CSF examination, which was positive for adenocarcinoma cells. Even this patient did not have brain parenchymal metastasis. He was started on erlotinib and weekly intrathecal MTX. He received 10-12 mg twice a week for 4 weeks. Consolidation: 10-12 mg every week for 1 month. His symptoms of drowsiness, altered behavior and ptosis and performance status gradually improved after that. However after 2 months, patient was lost to follow-up.

Both these cases highlight the way isolated CSF metastasis can occur in patients with lung cancer. Though brain parenchyma does not show parenchymal disease on imaging one should have a high index of suspicion and perform at least three CSF analyses if the clinical setting is appropriate. Furthermore, in patients with EGFR mutation positive lung cancer with isolated CSF metastasis, addition of tyrosine kinase inhibitor may lead to much improved outcomes. Importantly patients with CSF disease derive significant palliation in symptoms after intrathecal therapy as demonstrated in above cases.

DISCUSSION

Epidemiology

It is estimated that eventually up to 3-5% of patients with solid tumors develop carcinomatous meningitis. Commonly, breast > lung > melanoma have a tendency to spread to the CSF.^[1-3] In lung cancer brain metastases occur in almost 30% of patients, while carcinomatous meningitis occurs in only 5% of patients.^[3] Though most patients who present with carcinomatous meningitis have a past history of treated malignancy or active malignancy, some patients have their cancer diagnosed after diagnosis of carcinomatous meningitis.^[4]

Clinical presentation: Presentation is varied. Patients may present with headache, back pain or radicular pain, vomiting, photophobia, features suggestive of cranial nerve involvement such as diplopia, facial palsy, hearing loss and hoarseness of voice, dysphagia and altered taste. Occasionally, patients present with seizures, gait disturbances, confusion and memory loss. Confusional state and dementia are usually

difficult to attribute to carcinomatous meningitis initially and requires a high degree of suspicion to diagnose.^[5-8]

DIAGNOSIS AND WORK UP

CSF cytology remains the gold standard in diagnosis of carcinomatous meningitis. Though an insensitive test, repeated testing increases the yield of a positive result in up to 90% of patients of carcinomatous meningitis. A high opening pressure (>200 mm H₂O), elevated protein (>60 mg/dl), reduced glucose levels (<50 mg/dl), the point towards the diagnosis however are not conclusive. It is recommended that at least 10 ml of CSF is to be collected for analysis followed by early processing of the sample to prevent degeneration of cells and sampling from the site of symptomatic radiologic disease (lumbar or ventricular).^[9]

MRI with gadolinium enhancement is recommended ideally before the lumbar puncture to localize the disease sites in the neuraxis as indicated by abnormal contrast enhancement. Furthermore, MRI done after the lumbar puncture can lead to false positive contrast enhancement on MRI.^[10] MRI shows uptake in up to 40-60% of patients.^[5]

CSF pathways should be assessed before giving intrathecal chemotherapy in patients with solid tumor carcinomatous meningitis. It is done by nuclear flow study. A third of patients with carcinomatous meningitis have abnormal flow studies. In such patients, intrathecal chemotherapy can lead to unexplained toxicity due to concentration of cytotoxic agents at the site of block.^[11,12]

Treatment

Includes multidisciplinary approach of surgical (omaya reservoir placement, ventriculo-peritoneal [V-P] shunt placement), radiation (RT) (RT to high burden sites), intrathecal and systemic chemotherapy. Decision to treat carcinomatous meningitis should be carefully taken, informed collective decision, since outcomes are poor overall. In a recent study were authors studied 91 consecutive patients with carcinomatous meningitis median survival was only 3.6 months.^[13] Patients with good performance status with less disease burden are most likely to benefit from therapy. Furthermore, a recent study stated that treatment with RT and concomitant systemic therapy and intrathecal chemotherapy added to the survival benefit.^[14] Although cure is not in sight, quality-of-life is improved and survival prolonged with therapy.^[14] Intraventricular reservoir is known to add survival advantage.^[15] Above cases highlight the role of intrathecal treatment and its effect on palliation.

Radiotherapy

RT to high disease burden sites is known to be beneficial symptomatically, however overall survival is not affected.^[16]

Radiotherapy has also been explored to relieve the sites of CSF block detected on radio nucleotide flow study to facilitate intrathecal chemotherapy.^[17]

Intrathecal therapy

MTX and cytosine arabinoside (Ara-C) were historically the mainstays of medical treatment for carcinomatous meningitis caused by any primary cancer. However both are not known to be very active in lung cancer. However MTX and cytarabine remain the main drugs used in intrathecal therapy in carcinomatous meningitis. Topotecan has also been used with equivocal results.^[18] Liposomal Ara-C is another option with similar results in efficacy, but with the advantage of reduced frequency of intrathecal therapy.^[19] Following schedules have been recommended.

MTX induction: 10-12 mg twice a week for 4 weeks.
Consolidation: 10-12 mg every week for 1 month and then every 2 weeks for 2 months. Maintenance: 10-12 mg every 4-8 weeks. If MTX is delivered intraventricularly, consider 50% of dose reduction.

Liposomal cytarabine induction: 50 mg every 14 days for a total of 2 doses (weeks 1 and 3) Consolidation: 50 mg every 14 days for 3 doses (weeks 5, 7 and 9), followed by an additional dose at week 13. Maintenance: 50 mg every 28 days for 4 doses (weeks 17, 21, 25 and 29). If cytarabine is delivered intraventricularly, consider a dose reduction of 50%.

Topotecan Induction: 0.4 mg twice/week for 6 weeks.
Consolidation: 0.4 mg twice/week for 6 additional doses
Maintenance: 0.4 mg twice monthly for 4 months and then monthly thereafter.

Intravenous chemotherapy

If patient is fit enough intravenous chemotherapy with pemetrexed is recommended if patient has not already received the drug. There is some evidence in preclinical studies of its efficacy.^[20] Other conventionally used drugs like high dose cytarabine and high dose MTX have a minimal activity in non-small cell lung cancer.

Role of targeted therapy

In patients with EGFR mutation oral tyrosine kinase inhibitors are particularly effective in carcinomatous meningitis. Higher doses of erlotinib/gefitinib in patients with carcinomatous have improved results.^[21] Another study stratified patients with EGFR mutation and carcinomatous meningitis based on the type of mutation and reported that if deletions in exon 19 did better than deletion in exon 21 (Median survival of 11 months vs. 7.1 months).^[13]

Supportive care

Increase in intracranial pressure (ICP) is seen in most patients with carcinomatous meningitis. It can be controlled with steroids-dexamethasone starting at 8 mg twice a day usually effective. Steroids have to be tapered fast to most effective dose. If steroids cannot control symptoms of increased ICP, then V-P shunt is safe and efficacious as a palliative tool.^[22] However V-P shunt is pursued only when no further intrathecal chemotherapy is planned since intrathecal therapy will drain into the abdominal cavity if V-P shunt is *in situ*.

Pain should be controlled with adequate analgesia.

Anticonvulsants are not used prophylactically. Levetiracetam or clonazepam for controlling seizures if they develop.

Serotonin reuptake inhibitors like citalopram are beneficial for depression. Excessive fatigue can be treated with stimulant medications such as modafinil and methylphenidate.

Toxicity with intrathecal therapy and its management: Complications of intrathecal chemotherapy include ventricular reservoir infection, malposition and obstruction. Infections are managed as for standard meningitis guidelines. Myelosuppression can occur after administration of intrathecal chemotherapies and folinic acid rescue can be used to overcome this complication of intrathecal MTX. Rarely chemical meningitis can occur. This is managed with symptomatic therapy and analgesics. Rarely treatment-related neurotoxicity occurs and may result in a symptomatic sub-acute leukoencephalopathy or myelopathy.

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How to cite this article: Kumar DS, Noronha V, Joshi A, Jain H, Prabhaskar K. Carcinomatous meningitis in non-small cell lung cancer: Palliation with intrathecal treatment. *Indian J Med Paediatr Oncol* 2014;35:75-8.
Source of Support: Nil. **Conflict of Interest:** None declared.