Indian Journal of Surgical Oncology (June 2020) 11(2):308–312
https://doi.org/10.1007/s13193-020-01071-0

ORIGINAL ARTICLE

Classification of Leptomeningeal Metastases from Solid Organ Malignancies and Clinical Outcomes: Series from a Cancer Research Centre

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Received: 17 August 2019 / Accepted: 1 April 2020 / Published online: 17 April 2020

Abstract

Leptomeningeal metastases (LMs) are a critical neurological manifestation of solid organ malignancies. Early diagnosis and prompt treatment is necessary to improve outcomes. We classified LM on the basis of cytological or histological and imaging studies. A total of 14 patients of LM from solid organ malignancies diagnosed between July 2016 and December 2018 were included in the series. LM was classified based on cerebrospinal fluid (CSF) cytology and magnetic resonance imaging (MRI) findings. Survival outcomes were noted. LM from carcinoma of breast and lung accounted for most of the cases. Type I LM was seen in 12 patients while 2 accounted for type II LM. Median overall survival (OS) was 40.5 days. Newer-generation tyrosine kinase inhibitor (TKI) therapy seems promising in the treatment of LM. Classification of LM based on cytology/histology and imaging findings allows early diagnosis and treatment. Newer-generation TKIs should be used for the treatment of LM if indicated.

Keywords Leptomeningeal metastases · Tyrosine kinase inhibitor · Quality of life · Intrathecal chemotherapy

Introduction

Leptomeningeal metastases (LMs) are an uncommon manifestation of late-stage solid organ malignancies. Various synonyms have been used to describe LM from solid organ malignancies like neoplastic meningitis, carcinomatous meningitis, and meningeal carcinomatosis. Metastases arise from infiltration of the leptomeninges, namely, pia and arachnoid mater and sub-arachnoid space by malignant cells being shed off from an extrameningeal primary. This entity was first described by Eberth CJ [1]. Incidence of LM has been reported as 5 to 8% although with the advancement in oncology, more patients are being diagnosed with LM as they live longer [2]. Despite advancements in diagnostic and therapeutic oncology, overall survival and prognosis in LM remains dismal as blood-brain barrier effectively shields chemotherapeutic agents to reach central nervous system in therapeutic concentrations.

Although, LM can be seen arising from virtually any solid organ malignancy, cancer of breast, lung, gastrointestinal tract, and melanoma constitute majority of cases [3]. Clinical manifestations can be overt like seizures, encephalopathy, cranial nerve palsies, and radicular pain or minimal in the form of subtle confusion, forgetfulness, vertigo, or headache. A high index of suspicion should be kept in mind to diagnose LM whenever minimal or subtle neurological symptoms and signs are encountered. Prompt diagnosis of LM allows potentially more effective treatment prior to development of permanent neurological damage, thus improving quality of life (QOL) and survival in such patients. A retrospective series of LM is presented here. We aimed to classify LM as per the diagnostic criteria laid by Le Rhun et al. which can lead to improved diagnosis and early management [4]. Special attention has been given to newer generation of targeted agents which are able to penetrate the blood-brain barrier and are thus effective in the treatment of LM.

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Table 1 Baseline characteristics. *ECOG* Eastern cooperative oncology group, *GCS* Glasgow coma scale

Baseline characteristics	($n = 14$)
Mean age at diagnosis	58.7 years(38–78)
Males	6
Females	8
Primary diagnosis	
Carcinoma breast	6
Adenocarcinoma lung	3
Adenocarcinoma stomach	2
Hepatocellular carcinoma	1
Adenocarcinoma rectum	1
Neuroendocrine carcinoma rectum	1
Low GCS (< 15)	8
Performance status (ECOG)	
1	0
2	1
3	8
4	5
LM as initial manifestation of cancer	3

Patients and Methods

This is a retrospective study of the patients of LM from solid organ malignancies diagnosed between July 2016 and December 2018. Records were retrieved from computerised patient record system. Age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary diagnosis, Glasgow coma scale (GCS), symptoms and signs, and focal neurological deficits (FNDs) were noted. Magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis findings were noted. LM was classified as per the criteria laid by Le Rhun et al. [4]. Treatment details and survival outcomes in terms of improvement in PS, improvement in symptoms/signs, and overall survival were noted. Descriptive statistics was used to analyse the results. The study was approved by institutional ethical committee.

Results

Baseline characteristics are shown in Table 1. A total of 14 patients (6 males and 8 females) of solid organ malignancies were diagnosed with LM during the study period. Mean age at the time of diagnosis was 58.7 years (38–78 years). The primary sites of disease identified were carcinoma breast in 6 cases, adenocarcinoma lung in 3 cases, adenocarcinoma stomach in 2 cases, and 1 case each of hepatocellular carcinoma, adenocarcinoma rectum, and neuroendocrine carcinoma rectum. Most of the patients presented to us with poor PS. Three patients including 2 of carcinoma breast and 1 of adenocarcinoma lung had LM as initial manifestation of malignancy.

GCS was found to be low (< 15) in 8 patients. Headache, vomiting, and altered sensorium were the most common presenting features. FNDs in the form of cranial nerve (CN) palsies and paraparesis were found in 5 patients. CSF malignant cytology was positive in 12 patients, while imaging findings consistent with LM were seen in 9 patients. We classified LM based on 2 major criteria as per imaging and CSF studies [4]. Five patients had Type IA, 4 had type ID, 2 had type IC, and 1 patient each had type IB, IIC, and IID disease (Table 2). CSF lactate dehydrogenase (LDH) and protein was elevated in 14 and 9 patients, respectively. Hypoglycorrhachia was found in 7 patients (Table 3).

Table 2 Diagnostic studies. *CN* cranial nerves, *CSF* cerebrospinal fluid, *LM* leptomeningeal

Case no.	Clinical findings	Glasgow Coma Scale	Imaging studies (MRI)	CSF (malignant cells)	Classification
1	Encephalopathy, CN palsies, paraparesis	12/15	Linear and nodular LM disease	Negative	Type IIC
2	Encephalopathy, seizures	8/15	No LM disease	Positive	Type ID
3	Headache, vomiting, CN palsies	15/15	No LM disease, hydrocephalus	Positive	Type ID
4	Encephalopathy, CN palsies	14/15	No LM disease	Positive	Type ID
5	Neck pain, backache,	15/15	Linear LM disease	Positive	Type IA
6	Encephalopathy	12/15	Linear LM disease	Positive	Type IA
7	Encephalopathy, CN palsies	9/15	No LM disease	Negative	Type IID
8	Headache, vomiting	15/15	No LM disease	Positive	Type ID
9	Encephalopathy	12/15	Linear LM disease	Positive	Type IA
10	Headache, vomiting	15/15	Linear LM disease	Positive	Type IA
11	Headache	13/15	Nodular LM disease	Positive	Type IB
12	Headache, vomiting	15/15	Linear LM disease	Positive	Type IA
13	Headache, vomiting, CN palsies	13/15	Linear and nodular LM disease	Positive	Type IC
14	Headache, vomiting	15/15	Linear and nodular LM disease	Positive	Type IC

Table 3 CSF biochemistry. *CSF* cerebrospinal fluid, *LDH* lactate dehydrogenase

CSF biochemistry	No. (%)
Elevated LDH	14 (100%)
Elevated protein	9 (64.2%)
Hypoglycorrhachia	7 (50%)

Triple-agent intrathecal (IT) chemotherapy (methotrexate, cytarabine and hydrocortisone) and single-agent IT chemotherapy were administered in 4 and 10 patients, respectively. Two patients also received tyrosine kinase inhibitor (TKI) therapy, namely, ceritinib and osimertinib. Four patients were able to take systemic chemotherapy after improvement in PS. Symptomatic improvement was noticed in 7 patients while improvement in PS was noticed in 5 patients. Median OS was 40.5 days (10–321) (Table 4).

Discussion

A recent classification of LM based on cytology or histology and typical neuroimaging findings has been proposed by Le Rhun et al. A cytologically or histologically proven disease is defined as type I LM while type II disease complies with clinical and neuroimaging findings in the absence of cytological or histopathological evidence. Neuroimaging findings can be further subdivided into A, B, C, and D categories based upon linear, nodular, both, or no abnormalities, respectively. The plausibility of LM based on these findings can be assigned as "confirmed (Type I)," "probable (Type II)," "possible (with typical clinical signs only)," or "no evidence for (without type I or II features and no clinical signs)." LM can be treated with relative certainty when "confirmed" or "probable." Further diagnostics is required for "possible" or "no evidence for" cases. Patients falling into the category of no evidence for should not receive LM-directed cancer-specific treatment. Further evaluation is warranted in cases of high clinical suspicion [4]. Our institutional protocol necessitates for an MRI study prior to proceeding to lumbar puncture and CSF examination in a suspected case of carcinomatous meningitis. We demonstrated type I (confirmed) disease in 12 patients while type II (probable) and possible disease was seen in 1 patient each.

Breast cancer, lung cancer, and gastrointestinal tract cancer account for most of the cases in the available literature [5, 6]. Our series also revealed similar trend and LM from breast cancer constituted 42.8% of the cases.

FNDs can be seen associated with LM whenever there is delay in presentation or diagnosis or if the disease biology is aggressive. Pan Z et al. in their study demonstrated FNDs in 56% of cases diagnosed with LM associated with solid tumours. FNDs were mostly associated with CN palsies [7]. We found CN palsies in 5 (35%) cases while 1 patient presented with rapid onset paraparesis. Neurological recovery was demonstrated in 3 patients with treatment while 2 patients suffered permanent deficits. Prompt diagnosis and treatment is thus necessary in order to preserve QOL and reverse any neurological deficit.

Table 4 Treatment and survival outcomes. *CNS* central nervous system, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *IDC* invasive ductal carcinoma, *IT* intrathecal, *OS* overall survival, *PS* performance status, *TKI* tyrosine kinase inhibitor, *TNBC* triple-negative breast cancer

Case no	Primary diagnosis	CNS therapy	Improvement in symptoms	Improvement in PS	Concurrent systemic therapy	OS (days)
1	IDC breast ER+, HER2−	Triple-agent IT	Yes	Yes	Yes	321
2	Adenocarcinoma rectum	Single-agent IT	No	No	No	19
3	Adenocarcinoma lung, ALK+	Single-agent IT + TKI	Yes	Yes	Yes	223
4	IDC breast, TNBC	Triple-agent IT	Yes	Yes	Yes	53
5	Adenocarcinoma stomach	Triple-agent IT	Yes	Yes	Yes	156
6	Adenocarcinoma stomach	Single-agent IT	Yes	No	No	30
7	Hepatocellular carcinoma	Single-agent IT	No	No	No	35
8	IDC breast, ER+, HER2+	Single-agent IT	Yes	No	No	23
9	IDC breast, ER+, HER2−	Single-agent IT	No	No	No	10
10	IDC breast, TNBC	Single-agent IT	No	No	No	86
11	IDC breast, ER+, HER2−	Single-agent IT	No	No	No	14
12	Adenocarcinoma lung, T790M+	Single-agent IT + TKI	No	No	Yes	33
13	Adenocarcinoma lung	Single-agent IT	No	No	No	46
14	Neuroendocrine carcinoma rectum	Triple-agent IT	Yes	Yes	Yes	66

We used both single-agent (8 cases) and triple-agent (4 cases) IT chemotherapy. The commonly used institutional protocol is to deliver IT chemotherapy twice weekly for 4 weeks followed by weekly maintenance therapy. Choice of the agent or single vs multi-agent therapy depends upon physician's preference. Neither agent-specific therapy nor single vs multi-agent therapy has demonstrated any superiority [8, 9].

Median OS in our study was only 40.5 days and shows the aggressive nature of the disease. Median OS in LM is very poor and varies from few weeks to 6 months. LM from carcinoma breast has a relatively better survival as this responds better to IT chemotherapy [10]. Most of our patients demonstrated poor PS which is one of the most important prognostic variables [8, 11]. However, in the era of TKI therapy, patients can be expected to live longer as some of the newer-generation TKIs are able to cross blood-brain barrier and physically reach these metastases [12]. This has become the emerging focus of current research in the development of therapies for LM and other brain parenchymal metastases. Precision therapies formulated to enter CSF and target the metastases based upon the specific mutation allow better OS and safety profiles over non-selective agents. These agents include ALK inhibitors like ceritinib, alectinib, and brigatinib; ROS-1 inhibitor lorlatinib; and T790M inhibitor osimertinib [13–15].

A Case from our Series Is Worth Mentioning

Case No 3. patient was diagnosed as a case of metastatic adenocarcinoma lung. Molecular diagnostic study revealed EML4-ALK rearrangement, and he was offered crizotinib therapy. Patient achieved a progression-free survival of 9 months. He subsequently presented to us with headache, vomiting, diplopia, and diminution of vision in the right eye. Brain MRI study and CSF examination were consistent with type ID LM. He was administered IT single-agent methotrexate chemotherapy for 3 weeks, however without any improvement. IT was stopped and subsequently, he received ceritinib. He showed a remarkable improvement within 1 week of therapy. FND reversed and his PS improved. Response was sustained for a period of 6 months after which he again relapsed and succumbed to his illness.

Conclusions

LM from solid organ malignancies is a situation of crisis. A high index of suspicion should be kept in mind whenever subtle neurological symptoms and signs are encountered as prompt therapy often leads to increased QOL and survival. Classification of LM based on cytology/histology and imaging findings allows early diagnosis and treatment [4]. This should be accepted in routine clinical practice. Although, median survival is still poor with IT chemotherapy, an honest search for an agent like TKIs should be done if clinically indicated as these agents have shown to penetrate CNS with improvement in QOL and overall survival. Overall outcome with these agents looks encouraging.

Author Contributions DS, LA, and RS were involved in data collection. DS and MW wrote the manuscript. DS, LA, and RS approved the final manuscript.

Compliance with Ethical Standards

The study was approved by institutional ethical committee.

Conflict of Interest The authors declare that they have no conflict of interest.

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