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ORIGINAL ARTICLE

Outcomes and clinical features of leptomeningeal carcinomatosis: A single center experience

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ABSTRACT

Objective: The aim of this study was to identify the clinical features and prognostic factors of cancer patients with leptomeningeal carcinomatosis (LMC) in a single center.

Patients and Methods: Patients 18 and older who had LMC diagnosis between 2013 and 2018 at Medical Oncology Department, Antalya Education and Research Hospital, Health Sciences University were included into the study. Their clinical features, treatment approaches, overall survival, survival after LMC diagnosis and prognostic factors on survival were retrospectively investigated.

Results: Sixteen solid cancer patients included in the study. The median time from primary tumor diagnosis to LMC diagnosis was 6 months (range, 1-180 months). The median time from LMC diagnosis to death was 1.5 months (range, 1-14 months). The median overall survival for the entire population was 11 months (95%CI 5.7-16.3). Age (p=0.6), gender (p=0.51), metastases areas (for liver metastases p=0.95, for lung metastases p=0.26, for bone metastases p=0.82), The Eastern Cooperative Oncology Group Performance Status (ECOG PS) (p=0.18), treatment type of LMC (only radiation therapy (RT) p=0.33; RT followed by intrathecal methotrexate (IT MTX) (p=0.35), RT type (p=0.76) and time from primary tumor diagnosis to LMC diagnosis (p=0.50) did not show prognostic effect on overall survival after LMC diagnosis.

Conclusion: Overall survival after LMC diagnosis is too short to see the effect of treatment modalities. Our study did not find any favorable or unfavorable prognostic factor on survival after LMC diagnosis.

Keywords: Leptomeningeal carcinomatosis, Survival, Prognostic factors

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Introduction

Leptomeningeal carcinomatosis (LMC) is a fatal complication of systemic cancer in which cancer cells seed through meninx and cerebrospinal fluid (CSF). Incidence of LMC in solid cancers vary from 1% to 10% [1,2]. LMC is mostly seen in breast cancer patients [3]. It shows a poor prognosis with median survival of 14 weeks for lung cancer [1], 7 weeks for gastrointestinal cancers [2], 12 weeks for breast cancer [4]. Overall survival for LMC of both solid and hematopoietic cancers was 12 weeks [4]. Standard diagnostic approach is the sampling of CSF and demonstration of cancer cells. But the sensitivity of sampling is poor due to high false negative result rates and only 55% of patients with LMC has positive cytology at initial examination [5]. Technical development in neuroradiology resulted in increased LMC diagnosis rates with MRI by finding meningeal enhancement [3]. The treatment options of LCM are mainly the same for all types of cancer but incidence and prognosis change according to histology of primary cancer. The survival differences cannot be explained or predicted with the present data. Mostly symptomatic treatments for headache, nausea, vomiting and back pain are performed. Intrathecal (IT) chemotherapy, whole brain radiotherapy (WBRT) and/or site specific radiotherapy are more specific therapeutic options [6,7]. Thiotepa, methotrexate and cytarabine are commonly used agents for IT route [7]. Despite the fact that central nervous system (CNS) is a privileged site and blood-brain-barrier limits the influx of cytotoxic drugs, systemic treatment in breast cancer and lung cancer patients with LMC showed clinical benefit in 15.8% of patients [8]. There are limiting retrospective studies evaluating survivals and prognostic factors in LMC patients. The aim of this study was to identify the clinical features and prognostic factors of cancer patients with LMC from a single center.

Patients and Methods

Study Design and Patients

Cancer patients aged ≥18 year-old with cytologically proven LMC between 2013 and 2018 at Medical Oncology Department, Antalya Education and Research Hospital, Health Sciences University were included into the study. Medical records of 16 patients were retrieved and retrospectively analyzed. The study was approved by the Health Sciences University, Antalya Education and Research Hospital Clinical Research Ethics Committee on 21st February , 2019 (approval number:2019-045, 6/2). Patients with primary CNS tumors and hematologic malignancies were excluded. Clinical features of LMC patients with disseminated solid cancers and their prognostic factors for survival were retrospectively investigated.

Statistical Methods

Statistical analysis was made using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Descriptive analyses were presented using median (min-max) or n (%), where appropriate. Overall survival (OS) was estimated using the Kaplan-Meier method. The log-rank test was used to compare survival differences. A univariate Cox proportional hazards regression model was used to identify prognostic factors. Hazard ratio, with corresponding 95% confidence intervals (95% CIs), was reported. A p-value of less than 0.05 was considered statistically significant.

Results

Sixteen patients who had diagnosis of LMC at a single center between 2013 and 2018 were included into the study. Median age of LMC onset was 53 years (range, 23-72 years). There were 7 male and 9 female patients. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) was <2 in 3 patients (18.8%) while it was ≥2 in 13 patients (81.2%) for LMC. Clinical demographics, primary tumor histology and treatment details are presented in Table I. The median time from primary tumor diagnosis to LMC diagnosis (TPM) was 6 months (range, 1-180 months). The most common clinical presentations were cerebral symptoms such as headache (68.8%) and mental confusion (56.3%). Presenting symptoms were presented in Table I and Figure 1. The median time from LMC diagnosis to death (TMD) was 1.5 months (range, 1-14 months). The median overall survival (m OS) for the entire population was 11 months (95%CI 5.7-16.3) (Figure 2).

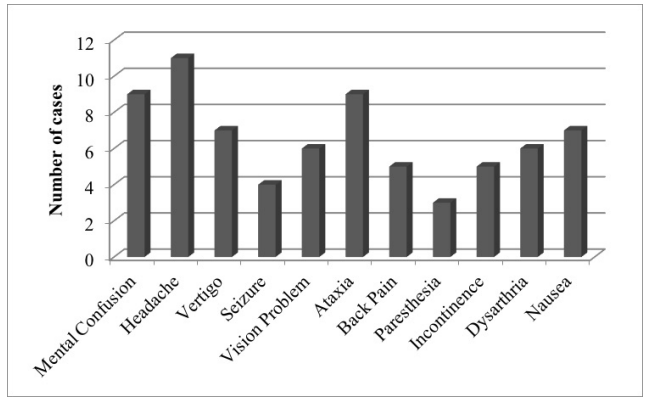

Figure 1. Presenting symptoms of LMC

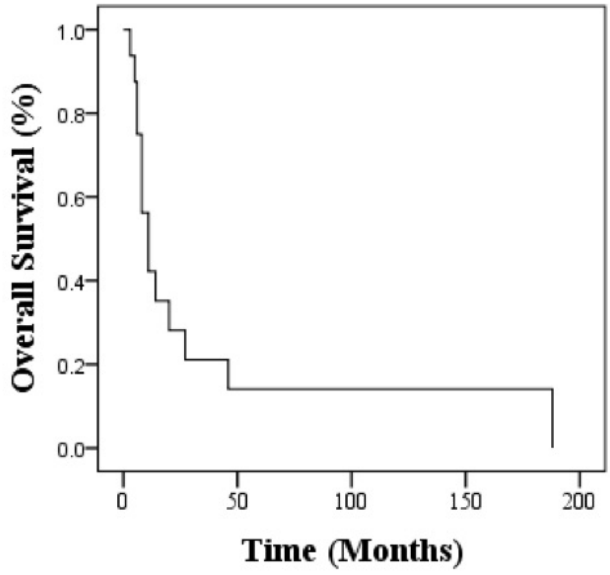

Figure 2. Median OS after primary cancer diagnosis in general population was 11 months (95% CI, 5.7-16.3)

After LMC diagnosis only two patients received best supportive care, 8 patients (50%) had only radiotherapy (RT) and 6 patients had sequential RT and intrathecal methotrexate (MTX) (Table I). There were no OS differences between cranial RT and craniospinal RT groups (p=0.71) (Figure 3), also IT MTX treatment did not prolong the survival after LMC treatment (p=0.75) (Figure 4). Age (HR, 0.988; 95%CI, 0.947-1.032, p=0.6), gender (HR1.459; 95%CI, 0.479-4.444, p=0.51), metastatic areas (for liver metastases p=0.95, for lung

metastases p=0.26, for bone metastases p=0.82) (Table II), ECOG PS at LMC diagnosis (HR,2.976; 95%CI, 0.602-14.718, p=0.18), presence of synchronous parenchymal mass (HR,0.858; 95%CI, 0.262-2.810, p=0.80), treatment options for LMC (only RT p=0.33; RT and IT MTX p=0.35), RT type (p=0.76) and time from primary tumor diagnosis to LMC diagnosis (TPM) (HR, 1.458; 95% CI, 0.484-4.392, p=0.50) did not show prognostic effect on overall survival after LMC diagnosis.

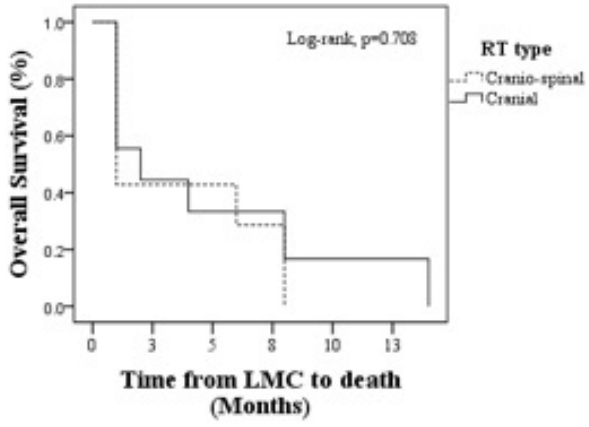

Figure 3. OS with craniospinal RT vs cranial RT

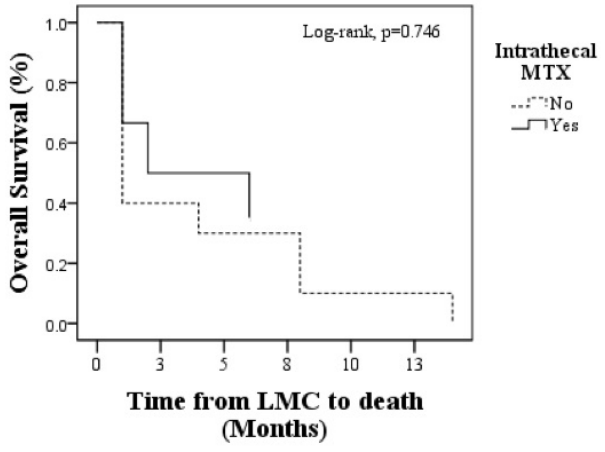

Figure 4. OS with implication of intrathecal MTX

Table I. Clinical Demographics

	n:16
Primary Tumor, n(%)	
Lung cancer	6 (37.5)
Breast cancer	3 (18.8)
Colon cancer	1 (6.3)
Medullary thyroid cancer	1 (6.3)
Gastric cancer	2 (12.5)
Endometrial cancer	1 (6.3)
Pancreas cancer	1 (6.3)
Nonseminomatous testis cancer	1 (6.3)
Metastatic disease, n(%)	
Liver metastases	4 (25)
Lung metastases	9 (56.3)
Bone metastases	9 (56.3)
RT Type	
Cranio-spinal	5 (31.25)
Cranial	9 (56.25)
LMC treatment	
No Treatment	2 (12.5)
RT	8 (50)
RT+Intrathecal MTX	6 (37.5)
Parenchymal Mass, n(%)	
Yes	11 (68.8)
No	5 (31.3)
Stage at diagnosis, n(%)	
Stage II	3 (18.8)
Stage III	2 (12.5)
Stage IV	11 (68.8)
MRI Findings at LMC diagnosis, n (%)	
Normal	5 (31.3)
Intracranial mass	3 (18.8)
Leptomeningeal thickening	6 (37.5)
Ventricular dilatation	2 (12.5)
Presenting Symptoms of LMC, n(%)	
Mental confusion	9 (56.3)
Headache	11 (68.8)
Vertigo	7 (43.8)
Seizure	4 (25)
Vision Problems	6 (37.5)
Ataxia	9 (56.3)
Back Pain	5 (31.3)
Paresthesia	3 (18.8)
Incontinence	5 (31.3)
Dysarthria	6 (37.5)
Nausea	7 (43.8)

RT. Radiothrapy, LMC: Leptomeningeal carcinomatosis, MTX: Methatrexate

Table II. Prognostic factors affecting OS after LMC diagnosis

Variables	HR (95%CI)	p
Age	0.988(0.947-1.032)	0.598
Gender (Ref=Female)	1.459(0.479-4.444)	0.506
Mental Confusion (Ref:Absent)	1.076(0.325-3.559)	0.905
Liver Metastases (Ref:Absent)	0.957(0.260-3.520)	0.947
Lung Metastases (Ref:Absent)	0.500(0.148-1.687)	0.264
Bone Metastases (Ref:Absent)	0.881(0.294-2.633)	0.820
LMC ECOG PS		
< 2 (Ref)	1	-
≥2	2.976(0.602-14.718)	0.181
Paranchymal Mass (Ref:Absent)	0.858(0.262-2.810)	0.801
LMC Treatment		
No treatment (Ref)	1	-
RT	0.429(0.079-2.339)	0.328
RT+Intrathecal MTX	0.429(0.073-2.512)	0.348
RT Type		
Cranio-spinal (Ref)	1	-
Cranial	0.846(0.283-2.530)	0.765
TPM		
≤6 (Ref)	1	-
>6	1.458(0.484-4.392)	0.502

TPM: time from primary tumor diagnosis to LMC diagnosis

Discussion

In recent studies, m OS after LMC diagnosis ranged from 0.7 months to 4.8 months [9-14], in our study m OS was 1.5 months which was similar to literature. Clinical presentation with cerebral symptoms were the most common symptoms in conformity with the literature [7,12,14]. But, in our study nature of the clinical symptoms were not found to have prognostic effect as Giglio et al's study [2].

Whereas, LMC was mostly seen in breast cancer patients in Western countries [7,9,10,12,14], Asian studies reported that LMC occurred most frequently in lung cancer patients [11,13]. Consistent with Asian studies, in our study, lung cancer was the most frequent type of cancer and breast cancer was the second most common one seen in LMC patients. In order to find out the ethnic differences in LMC, more population-based studies are needed worldwide.

LMC is a progressive disease that is resistant to current therapeutic options. What is important in LMC is to predict which patient will benefit from intensive treatment. Hyun et al., reported age under 55, female gender, high performance status and active treatment with RT and IT chemotherapy were favorable prognostic factors with m OS of 3 months (95% CI 2.7-3.3) [4]. Unlike this research, we did not find any association between survival and gender, ECOG PS, treatment types. Boogerd et al., searched IT chemotherapy benefit in breast cancer patients with LMC [15]. They concluded that addition of IT chemotherapy to standard cytotoxic treatment with involved field RT did not improve survival (median survival of IT patients was 18.3 weeks and 30.3 weeks for non-IT patients (p=0.32)) or neurological symptoms. Our study also showed no difference with the implication of IT MTX. On the contrary, Lee et al., reported favorable survival with the application of IT chemotherapy (17 weeks versus 8 weeks, p<0.001) [1]. Another two studies showed a trend in increased survival with the application of treatment regardless of the treatment type [2,4].

El Shafie et al., reported that patients with good clinical performance showed an improved m OS of 28.3 weeks, whereas, patients with poor clinical performance showed a m OS of 9.3 weeks. (p<0.001) [16]. Patients with good clinical performance also showed improvement in neurological functional scale as prognostic factor for superior OS. Another report by El Shafie et al., also showed that there was no prognostic significance of primary tumor histology on OS (including 39% breast cancer, 28% lung cancer, 8%gastrointestinal cancer, 6% malign melanoma, 5.5% prostat cancer) [17]. They showed that RT fields (cranial, cranio-spinal or spinal) did not influence the OS which was similar to our results.

While some previous studies did not find age as a prognostic factor like our study, some other studies found older age as a negative prognostic factor [2,4,6,15]. Good ECOG PS was found as a positive prognostic factor in many studies [1,4,6,7,13] whereas another study [2] had found no association between survival and ECOG PS like our study.

Time from primary tumor diagnosis to LMC (TPM) >67 weeks was reported to be independently associated with longer OS regardless of treatment type [7] but Giglio et al. [2] and Gwak et al. [6] found no association between survival and TPM like our study. In our study TPM was dichotomized by median value of 6 months and was not found as a prognostic factor.

Limitations of the current study were its retrospective nature which may cause selection bias owing to patients with poor performance and older age as they did not get any treatment. Due to retrospectivity we could not record neurological functional scale. In previous studies 21-31% of patients were reported to be LMC positive on magnetic resonance images only [4,12,18] but in our study only cytologically proven patients with LMC were included.

This limitation resulted in small number of patients being included in the study.

Conclusions

Overall survival after LMC diagnosis is too short to see the effects of treatment. Our study did not find any favorable or unfavorable prognostic factor on survival after LMC diagnosis. Initially, the nature of this rare disease must be investigated, though it is difficult to define the risk factors, the treatment must be guided accordingly. We believe that the right diagnosis leads to the appropriate treatment option for each individual patient.

Conflict of interest: None declared by the authors.

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