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RESEARCH ARTICLE

Lung Cancer with Leptomeningeal Carcinomatosis – Does intrathecal chemotherapy has a role? A Real Word Data approach using Trinetx

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ABSTRACT

Background: Lung cancer is one of the neoplasms that most frequently spreads to the meninges and currently there is no consensus or standard management of this condition. Intrathecal chemotherapy (IC) has been adopted as an attempt to reach disease control, however real-world data regarding the efficacy of this therapeutic approach is yet to be described in literature.

Aim: To evaluate the impact of intrathecal chemotherapy on overall survival (OS) of patients with lung cancer and leptomeningeal carcinomatosis in a contemporary and real-world setting.

Methods: Our study was performed by using TriNetX, a global health network dataset of electronic medical records of patients from 101 healthcare organizations around the world. We queried for patients with specific terms between January 2003 and March 2023 and performed a propensity score matching (PSM) analysis for cohort balancing. Cohort 1 enrolled patients submitted to IC while cohort 2 enrolled patients not receiving IC during their treatment pathway. OS was estimated by Kaplan–Meier and log-rank test was applied.

Results: After initial query and propensity score matching, 139 patients were selected in each cohort. Methotrexate (42%) and Cytarabine (32%) were the most frequent treatment received by patients and the most common sequence of treatment that patients followed during their treatment pathway. Median overall survival was 109 days in intrathecal chemotherapy (cohort 1) and 280 days in those who did not receive intrathecal chemotherapy (cohort 2), with a Hazard Ratio of 1.538 (95% CI 1.148 - 2.060) and log rank test providing a x^2 of 8.462 with p= 0.004.

Conclusions: In despite of the limitations inherent of a real-world data analysis, our study revealed that intrathecal chemotherapy had a detrimental effect on overall survival with increased risk of death among lung cancer patients having leptomeningeal carcinomatosis.

Introduction

Leptomeningeal Carcinomatosis (LC) was first described in the late 19th century [1,2], however its pathogenesis details were only elucidated recently. Like the pathophysiology of brain metastases, a multistep biological process also leads to LC, in which tumor cells must leave the primary tumor, travel through the vasculature and then reach a location where they can traverse into the CSF, widely known as seed and soil hypothesis[3]. Within the Cerebral Spinal Fluid (CSF), tumor cells upregulate the production of complement system (mainly c3), leading to disruption of the Blood Brain Barrier (BBB) and entry of plasma growth factors into CSF, promoting uncontrolled cell growth[4]. Leptomeningeal carcinomatosis is occasionally a terminal event for several solid tumors, with no efficacy treatment so far. According last EANO/ESMO guidelines, patients with metastatic solid tumors have a lifetime risk of developing leptomeningeal metastasis (LM) around 10% and contrastingly, CNS metastases reflects a median overall survival (mOS) of approximately 12 months while patients having LC are limited to 3 months[5].

Lung cancer is generally accepted as the most frequent cause of metastatic brain tumors (followed by breast and melanoma). It accounts for 30% to 60% of all brain metastases and occurs in 17% to 65% of patients with primary lung cancer[6,7]. Up to 5% of lung cancer patients might have LC, particularly in those with epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements[8]. Small cell lung cancer and adenocarcinoma are the most identified sources of brain metastases[9,10]. Current management of LC requires an individualized multidisciplinary approach including surgery for ventricular shunt placement, radiation therapy to bulky or symptomatic disease sites, systemic or intrathecal chemotherapy, more recently, immunotherapy[10]. The literature suggests better outcomes for patients with driver gene alterations such as EGFR mutations and ALK translocation when treated with target therapy.

Intrathecal chemotherapy is broadly prescribed in this scenario in attempt to reach symptoms control. To date, only weak evidence is available, diverging in terms of clinical outcomes[11,12]. **In an attempt to elucidate this dilemma**, real world data acquired from multicentric institutions could shed light on this issue. Our data were compiled into TriNetX[13] database by its software to describe the current patterns of treatment among lung cancer patients with leptomeningeal carcinomatosis and its respective impact on overall survival.

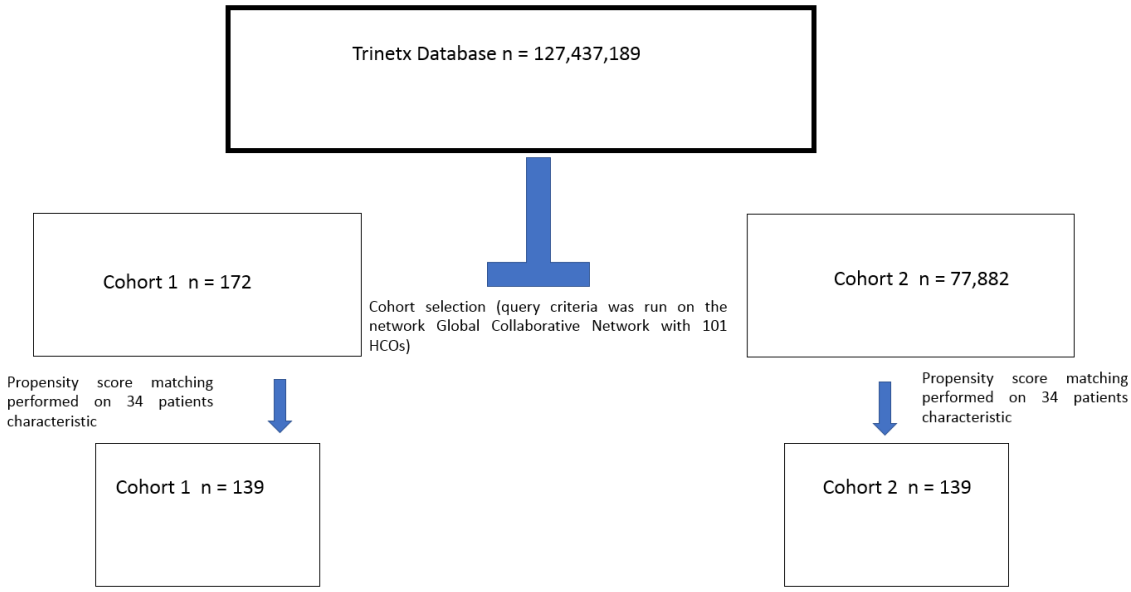
Methods

All data analytics procedures were done using TriNetX[13], a global federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) across large healthcare organizations (HCOs). This study was done under a set of HCOs grouped into a network called Global Collaborative Network. This network included 101 HCO(s). The analysis process includes two main steps: 1) Defining the cohort through query criteria; 2) Setting up and running the analysis. Setting up the analysis requires definitions for the index event, outcomes criteria, and time frame.

Cohort selection

Two cohorts were selected to evaluate the effect of IC over patients harboring leptomeningeal carcinomatosis originated from lung cancer. Cohort 1 enrolled patients submitted to IC while Cohort 2 enrolled patients not receiving IC during their treatment pathway. Cohort 1 query criteria was run on the Global Collaborative Network with 101 HCOs queried, 31 of them provided patient data. The final cohort included 172 patients who matched the query criteria listed in the table 1. Cohort 2 query criteria was also run on the same Global Collaborative Network with 101 HCOs queried and 89 of them provided patient data. Query criteria were listed in the table 2. Flow diagram of patient and data selection were depicted in Consort 1.

Consort 1. Flow diagram of cohort selection procedure



Index Event & Time Window Definitions

Our analysis included outcomes that occurred in the time window that started 1 day after the first occurrence of the index event (described at table 1 and 2). The index event only included events that occurred up to 20 years ago. Patients whose index event occurred 20 years or more ago were excluded. In this analysis, 16 patients in Cohort 1 and 3,186 patients in Cohort 2 were excluded because they met the index event more than 20 years ago.

Survival Analysis

The Kaplan-Meier Analysis estimated probability of the outcome at a respective time interval. In order to account for the patients who exited the cohort during the analysis period, and therefore should not be included in the analysis, censoring was applied. In this analysis, patients were removed from the analysis (censored) after the last fact in their record. The output summary included: Patients in each Cohort (count of patients meeting query criteria); Patients with Outcome (of the patients in the cohort, count of patients that had the outcome in the time window); Median Survival (the number of days when the survival drops below 50%); and Survival Probability at End of Time Window (the % survival at the end of the time window). In addition, Log-Rank test, Hazard Ratio and test for proportionality were performed. Outcome definition and settings for the performed analyses are outlined in table 3.

Propensity Score Matching

Propensity score matching was performed on 34 characteristics. In the Demographics category patients were matched on Current Age, Age at Index, Female, Male, Not Hispanic or Latino, Hispanic or Latino, Unknown Ethnicity, Unknown Race, White, American Indian or Alaska Native, Asian, Black or African American characteristics. In the Medication category patients were matched on data of therapy administered during treatment pathway: carboplatin, paclitaxel, etoposide, bevacizumab, pembrolizumab, nivolumab, osimertinib, cisplatin, docetaxel, erlotinib, afatinib, alectinib, gefitinib, methotrexate, pemetrexed, cytarabine, cytarabine liposome and thiotepa. In the Genomic category patients were matched on EGFR, ALK, MET, TP53 and KRAS genetic profile. Characteristics of the cohorts before and after matching are summarized in the table 4.

Treatment pattern analysis

We performed an analysis for treatment pattern across those who received intrathecal chemotherapy. A line of treatment included any treatment taken within 1 days of the index event. The line of treatment finished after any of the following events: (1) When a new treatment appears in the patient record after the first day, (2) When a patient dies, (3) When a patient's medical record ends and (4) When the analysis time window ends.

Results

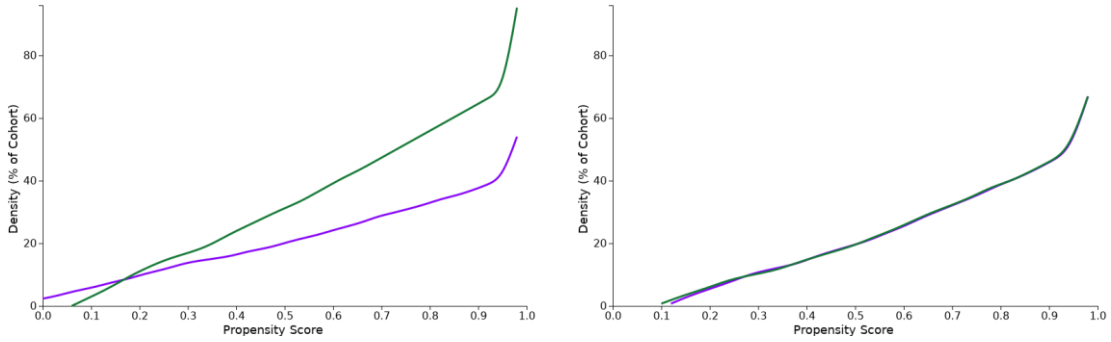
Trinetx[13] database comprises a total of 127,437,189 patients that were queried with aforementioned terms. Our analysis initiated with Cohort 1 represented by 172 patients and cohort 2 represented by 77,882 patients. After propensity score matching our cohort was reduced to Cohort 1

(N = 139) and cohort 2 (N = 139) with balanced characteristics (consort 1). The most relevant discrepancy that were not able to be balanced was MET mutation, cohort 1 (n= 10, 7,2%), cohort 2 (n=0, 0%) with p value of 0.001 standard difference of 0.394. Graphic 1 and Table 4

Graphic 1. Propensity score density function - Before and after matching (cohort 1 - purple, cohort 2 - green)

Cohort 1 and cohort 2 patient count before and after propensity score matching		
Cohort	Patient count before matching	Patient count after matching
1 - **IC Lung**	172	139
2 - **without IC Lung**	77,882	139

Propensity score density function - Before and after matching (cohort 1 - purple, cohort 2 - green)



Risk analysis for the outcome of death were performed on the cohorts after propensity score matching, **revealing a statistically significant increased risk** among those receiving intrathecal chemotherapy during clinical pathway. Cohort 1 risk of 73.4% and cohort 2 risk of 59.0% (95% CI=0.034, 0.254; z= 2.536 p<0.011). Graphic 2.

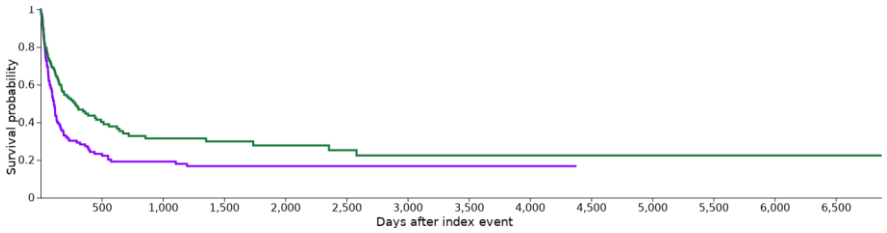
Kaplan - Meier survival analysis revealed a mOS of 109 vs 280 days between cohort 1 and 2, respectively (Survival probability at end of time window was 16.78% vs 22.43%). Log-Rank Test (x^2=21.443, p 0.004, with a hazard ratio of 1.538, 95% CI = 1.148 – 2.060) Graphic 3.

Graphic 3. Kaplan - Meier survival analysis

Kaplan - Meier survival analysis				
Cohort	Patients in cohort	Patients with outcome	Median survival (days)	Survival probability at end of time window
1 **IC Lung**	139	102	109	16.78%
2 **without IC Lung**	139	82	280	22.43%

	χ^2	Df	P
Log-Rank Test	8.462	1	0.004

	Hazard Ratio	95% CI	χ^2	df	P
Hazard Ratio and Proportionality	1.538	(1.148, 2.060)	0.137	1	0.712

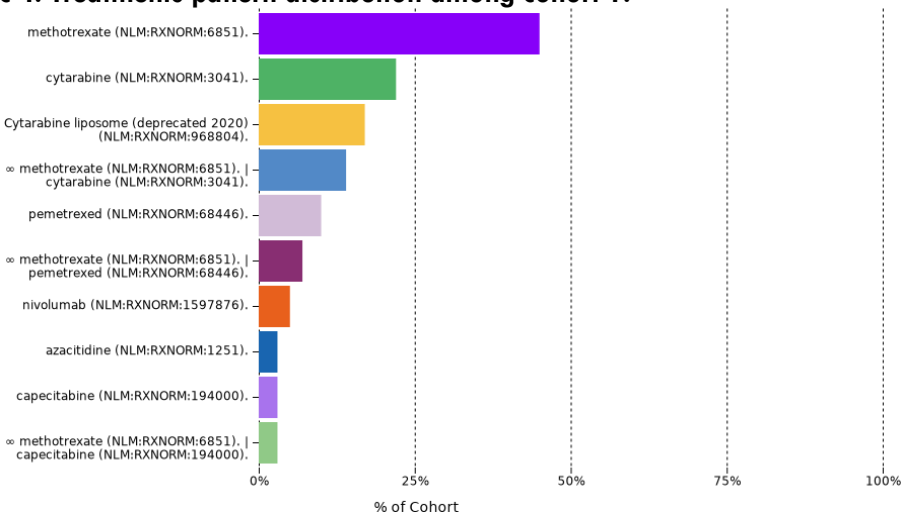


Number of instances

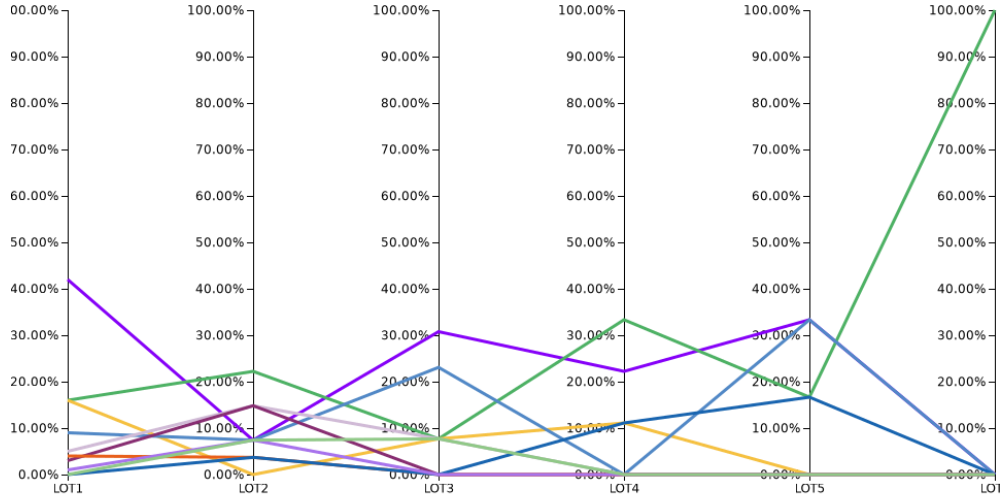
	Cohort	Patients in cohort	Patients with outcome	Mean	Standard Deviation	Median
1	**IC Lung**	139	102	1	0	1
2	**without IC Lung**	139	82	1	0	1

Treatment pattern analysis revealed that among those receiving intrathecal chemotherapy (cohort 1), 62 patients or 38.2% of the cohort, a clinical pathway were not available on medical record. The most common treatment received by patients, irrespective of the sequence, were Methotrexate (42%), Cytarabine or Cytarabine liposomal (32%), combination of Methotrexate + Cytarabine (9%) and others (17%). Graphic 4 and 5. **According to the sunburst diagram, graphic 6 supplement,** the most common sequence of treatment received by patients were: first line methotrexate followed by second line cytarabine. Due to the reduced number of patients, we couldn't compare the outcome of overall survival between treatments.

Graphic 4. Treatments pattern distribution among cohort 1.



Graphic 5. Line of treatments distribution



Discussion

Intrathecal chemotherapy has been historically adopted in patients harboring LC from lung cancers, however literature review highlights the controversial role of IC and currently it is not possible to describe a certain survival benefit or improvement in quality of life when IC is administered[14]. Our real word data analysis revealed that lung cancer patients receiving IC during their clinical pathway had inferior outcome regarding overall survival than those who were not submitted to this treatment modality, median overall survival was 109 days in intrathecal chemotherapy (cohort 1) and 280 days in those who did not received intrathecal chemotherapy (cohort 2), with a Hazard Ratio of 1.538 (95% CI 1.148 - 2.060) and log rank test providing a x^2 of 8.462 with p= 0.004. This fact comes in consonance with some authors[15,16] suggesting that addition of IC does not lead to survival benefit and is associated with an increased risk of neurotoxicity, confronting currently adopted protocols of IC for LC. It is noteworthy that our data were extracted from medical records in a retrospectively method and in despite of our efforts for cohort balancing with PSM with carefully selected terms of query, the results described in our study should be evaluated with caution and, treatment decision of indicating intrathecal chemotherapy must consider individual characteristics. Comparisons among the efficacy of different IC protocols were not feasible due to insufficient number of patients in the cohorts, however methotrexate seems to be the most adopted drug. In fact, few trials that compared head-to-head IC agents revealed that, in mixed tumor types, response to Methotrexate (MTX) was superior to combined MTX/Ara-C, but not statistically significant (61% v 45%; p > 0.10)[17]. However, combination of MTX and liposomal cytarabine was feasible in a small retrospective cohort[18]. Grossman and colleagues[19] evaluated IC in 52 patients with mixed primary tumors, assigned to receive IC MTX or thiotepa, revealing a non-statistically difference in mOS (15.9 weeks vs 14.1 weeks; p = 0.36). Additionally, the benefits of IC (MTX or ARA-C) compared to physician-chosen systemic therapy has also been evaluated, revealing that IC can be omitted safely as it did not improve patient outcomes and increased treatment-related toxicity[14]. In contrast to systemic chemotherapy, the effectiveness of IC may be limited, with no effect on survival compared with other treatment modalities and even associated with an increased rate of therapy-associated complications[20,21].

Our trial has not performed a cohort analysis with dual therapy (systemic and intrathecal) because our intent was to focus only in IC. Literature available revealed that patients who received IC liposomal cytarabine + conventional systemic therapy vs systemic therapy alone, the achieved mOS was 4.0 months in the control arm versus 7.3 months in the experimental arm (HR 0.85, 95% CI: 0.53–1.36; p=0.05), after adjusted, the differences were significant. However, the control arm was more heavily pretreated and systemic therapy was not standardized[22]. Additionally, IC thiotepa[23] and IC MTX[24] treatment combination was also tested, and some patients clearly had a long survival and authors suggests a clinical benefit. New drugs like pemetrexed were recently evaluated in a Chinese phase I/II trial, for EGFR mutated patients with LC who had failed targeted therapy; the clinical response was 84% (22 of 26 patients)

although clinical promising, this approach needs to be confirmed in phase III trial[25]. Recently published phase I trial demonstrates that concurrent Intrathecal and intravenous administration of nivolumab was safe with preliminary evidence of clinical benefit in a subset of patients[26]. Controversies on immunotherapy approach of LC exists since CSF penetrability of immune checkpoint inhibitors are relatively low, associated with a dysfunctionaland paucicellular immune repertoire in the leptomeninges. These factors highlight the need for innovative strategies to amplify immunotherapeutic responses in the spinal fluid.

Several other therapeutically active strategies are under investigation in patients with brain and leptomeningeal metastases[27], such as: Kirsten rat sarcoma viral oncogene homologue (KRAS) inhibitor adagrasib (NCT03785249); Lazertinib (third-generation EGFR-TKIs) in combination with amivantamab, an EGFR-MET bispecific antibody with immune cell-directing activity (NCT04965090); Tucatinib, a third-generation reversible and highly selective HER2 inhibitor (NCT03501979); HER2 antibody-drug conjugates, trastuzumab deruxtecan (T-DXd) (NCT04420598) and HER2 chimeric antigen receptor (CAR) T cells (NCT03696030). In our cohort only few patients has been treated with any target therapy and once this therapy were not delivered intrathecal, this analysis was not formally tested, however this group of patients might have better outcomes. Particulary targeting EGFR, the phase I BLOOM trial[28], in patients with LC pre-treated with a first or a second-generation tyrosine kinase inhibitor, meaningful outcomes were achived with 160mg of Osimertinib. LC response rate and duration of response by neuroradiologic BICR were 62% and 15.2 months, respectively. Median overall survival was 11.0 months. CSF Tumor cell clearance in CSF was achieved 28% of the patients (11 of 40 patients). Exposure to osimertinib-containing regimens (a known drug of higher CFS penetration), prior to development of LC, probably influence the natural history of LC disease with longer mOS independent of the systemic therapy administered after LC diagnosis[29], although more studies are required to clarify the Osimertinib high-dose usefulness in more advanced lines. Moreover, the combination of trametinib (MEKi, mitogen-activated protein kinase/ extracellular-signal-regulated kinase inhibitor) and osimertinib, to resensitize cells that become resistant to osimertinib are currently under evaluation[30]. Anaplastic lymphoma kinase gene rearrangement inhibitors (ALKi – Ceritinib; Brigatinib), has shown encouraging results in terms of disease control and survival[31,32]. Currently limited data are available regarding the use of immunotherapy in LC, however some case reports revealed promising results and phase I trial results were published[26] with a mOS of 4.9 months. Cancer Immunotherapy combinatorial strategies are under investigation for patients with LC, such as combination with Whole Brain Radiotherapy (NCT03719768), the multi-kinase VEGFR inhibitor lenvatinib (NCT04729348), encorafenib and binimetinib (NCT04511013), and EGFR inhibition (NCT04833205).

Two systematic reviews[33,34] highlighted the scarcity of high-quality data regarding the benefit of IC, and it is consensus that more accurate predictive and prognostic tools are required to improve treatment and to wisely choose those who benefit from IC approach. In 2017, the EANO-ESMO Clinical Practice Guidelines proposed a classification of LC in solid tumors. Type I (confirmed LC), verified cytologically or histologically and type II (probable or possible LC), based on the presence of clinical signs and neuroimaging[6]. The prognostic value of this classification was assessed in a retrospective study with better results for patients with type II LC compared to type I LC (median OS 4.5 months versus 2.4 months, respectively). Currently, the only response predictors in routine clinical practice during intrathecal therapy are: (i) CSF cytology clearance by 8 weeks[35], and (ii) serial MRI imaging, generally assessed 2 to 3 months following initiation of treatment[5]. Additionally, the administration of intrathecal, but also of systemic pharmacotherapy was associated with significantly increased survival only in type I LC, although the number of patients with type II were lower and there was a trend towards better survival with systemic pharmacotherapy[36]. One limitation of our study was the software analytical methodology not being able to provide clinical data for classification and stratification of LC according EANO-ESMO guideline. Various diagnostic tools and therapeutic efforts are currently under development aiming to improve survival as well as quality of life for patients with LC[37]. Cell-free tumor DNA (ctDNA) in the CSF for the diagnosis and characterization of actionable genomic alterations and monitor responses to therapy in patients with LC seems to be a valuable one[38].

Conclusion

According to our data and due to conflicting evidence from literature review, intrathecal chemotherapy seems to add relevant toxicity without evident clinical benefit and should be cautiously indicated considering individual clinical, radiological and pathological characteristics. The therapeutic strategy cannot

ignore a prognostic evaluation and multidisciplinary discussion and IC must not be adopted as a general protocol for every patient with lung cancer that evolves with leptomeningeal carcinomatosis. Tailored treatment according with genetic alterations might enhance efficacy in this scenario, especially for adenocarcinomas with LC. There is an urgent need of clinical practice implementation and validation of prognostic scores, such as EANO-ESMO, to properly select a subgroup of patients that could benefit. Prospective randomized controlled trials could pave the way for a definitive treatment guideline over this tragic disease evolution that carries one of the worst prognoses in oncology literature.

Conflicts of Interests Statement

The authors declare no conflicts of interests.

Funding Statement

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13. ©2023 TriNetX, LLC All Rights Reserved. The data used in this study was collected on April, 06th, 2023, from the TriNetX Global Collaborative Network, which provided access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from approximately 127 million patients from 101 healthcare organizations. Acessed April 06, 2023. https://live.trinetx.com/

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SUPPLEMENTARY MATERIAL

Table 1. Query Criteria for Cohort 1

Group 1					
	Lung without Carcinomatosis				
	must have		Diagnosis	UMLS:ICD10CM:C34	Malignant neoplasm of bronchus and lung
		And	Diagnosis	UMLS:ICD10CM:C79.3	Secondary malignant neoplasm of brain and cerebral meninges
		And	Procedure	UMLS:CPT:96450	Chemotherapy administration, into CNS (eg, intrathecal), requiring and including spinal puncture
	date constraint		between January, 1st, 2003 and March, 1st, 2023		

Table 2. Query Criteria for Cohort 2

Group 1					
	Lung with Carcinomatosis				
	must have		Diagnosis	UMLS:ICD10CM:C34	Malignant neoplasm of bronchus and lung
		And	Diagnosis	UMLS:ICD10CM:C79.3	Secondary malignant neoplasm of brain and cerebral meninges
	cannot have		Procedure	UMLS:CPT:96450	Chemotherapy administration, into CNS (eg, intrathecal), requiring and including spinal puncture
	date constraint		between January, 1st, 2003 and March, 1st, 2023		

Table 3. Outcome definition and settings for the performed analyses

Death			
	Outcome definition		
	Demographics	Deceased	Deceased
	Settings for the performed analyses		
	Risk analysis		including patients with outcome prior to the time window
	Kaplan - Meier survival analysis		including patients with outcome prior to the time window
	Number of instances analysis		including patients with outcome prior to the time window excluding patients with zero outcomes counts are grouped by date

Table 4. Cohort definition before and after propensity score matching (PSM)

Cohort 1 (N = 172) and cohort 2 (N = 77,882) characteristics before propensity score matching							
Demographics							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	Age	Current Age	65.7 +/- 14.1 70.7 +/- 11.3	155 74,681	100% 100%	<0.001	0.396
1 2	AI	Age at Index	57.8 +/- 13.2 64.4 +/-	155 74,681	100% 100%	<0.001	0.542

			11.3				
1 2	2106-3	White	107 47,516	69.0% 63.6%	0.162	0.115
1 2	1002-5	American Indian or Alaska Native	10 153	6.5% 0.2%	<0.00 1	0.354
1 2	F	Female	85 36,546	54.8% 48.9%	0.142	0.118
1 2	UN	Unknown Ethnicity	32 31,658	20.6% 42.4%	<0.00 1	0.481
1 2	2186-5	Not Hispanic or Latino	113 41,000	72.9% 54.9%	<0.00 1	0.382
1 2	2135-2	Hispanic or Latino	10 2,023	6.5% 2.7%	0.004	0.180
1 2	2054-5	Black or African American	10 7,350	6.5% 9.8%	0.157	0.124
1 2	M	Male	70 38,121	45.2% 51.0%	0.143	0.118
1 2	2131-1	Unknown Race	33 17,817	21.3% 23.9%	0.454	0.061
1 2	2028-9	Asian	10 1,787	6.5% 2.4%	0.001	0.198

Medication

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	40048	Carboplatin		42 8,447	27.1% 11.3%	<0.00 1	0.409
1 2	56946	Paclitaxel		23 3,909	14.8% 5.2%	<0.00 1	0.324
1 2	4179	Etoposide		21 4,091	13.5% 5.5%	<0.00 1	0.278
1 2	253337	Bevacizumab		22 1,157	14.2% 1.5%	<0.00 1	0.483
1 2	11202	Vincristine		17 164	11.0% 0.2%	<0.00 1	0.481
1 2	1547545	Pembrolizumab		10 1,920	6.5% 2.6%	0.002	0.188
1 2	1597876	Nivolumab		10 1,178	6.5% 1.6%	<0.00 1	0.250
1 2	1721560	Osimertinib		10 753	6.5% 1.0%	<0.00 1	0.290
1 2	2555	Cisplatin		18 3,065	11.6% 4.1%	<0.00 1	0.282
1 2	72962	Docetaxel		10 1,322	6.5% 1.8%	<0.00 1	0.237
1 2	337525	Erlotinib		16 1,109	10.3% 1.5%	<0.00 1	0.382
1 2	1430438	Afatinib		10 314	6.5% 0.4%	<0.00 1	0.336
1	17274	Alectinib		10	6.5%	<0.00	0.350

2	55			182	0.2%	1	
1 2	32813 4	Gefitinib		10 162	6.5% 0.2%	<0.00 1	0.353
1 2	6851	Methotrexate		41 548	26.5% 0.7%	<0.00 1	0.810
1 2	68446	Pemetrexed		30 3,386	19.4% 4.5%	<0.00 1	0.469
1 2	3041	Cytarabine		27 30	17.4% 0.0%	<0.00 1	0.647
1 2	96880 4	Cytarabine liposome (deprecated 2020)		10 10	6.5% 0.0%	<0.00 1	0.370
1 2	10473	Thiotepa		10 10	6.5% 0.0%	<0.00 1	0.370

Genomic

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	3236	EGFR		10 369	6.5% 0.5%	<0.00 1	0.330
1 2	427	ALK		10 302	6.5% 0.4%	<0.00 1	0.337
1 2	7029	MET MET proto-oncogene, receptor tyrosine kinase		10 187	6.5% 0.3%	<0.00 1	0.350
1 2	11998	TP53		10 328	6.5% 0.4%	<0.00 1	0.334
1 2	6407	KRAS		10 341	6.5% 0.5%	<0.00 1	0.333

Cohort 1 (N = 139) and cohort 2 (N = 139) characteristics after propensity score matching

Demographics

Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	Age	Current Age	66.2 +/- 13.9 66.9 +/- 13.8	139 139	100% 100%	0.653	0.054
1 2	AI	Age at Index	58.1 +/- 13.0 57.6 +/- 13.9	139 139	100% 100%	0.759	0.037
1 2	2106-3	White		96 82	69.1% 59.0%	0.080	0.211
1 2	1002-5	American Indian or Alaska Native		10 10	7.2% 7.2%	1	<0.001
1 2	F	Female		81 83	58.3% 59.7%	0.807	0.029
1 2	UN	Unknown Ethnicity		31 35	22.3% 25.2%	0.573	0.068
1 2	2186-5	Not Hispanic or Latino		101 96	72.7% 69.1%	0.509	0.079

1 2	2135-2	Hispanic or Latino		10 10	7.2% 7.2%	1	<0.001
1 2	2054-5	Black or African American		10 10	7.2% 7.2%	1	<0.001
1 2	M	Male		58 56	41.7% 40.3%	0.807	0.029
1 2	2131-1	Unknown Race		29 36	20.9% 25.9%	0.321	0.119
1 2	2028-9	Asian		10 10	7.2% 7.2%	1	<0.001
Medication							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	40048	carboplatin		36 38	25.9% 27.3%	0.786	0.033
1 2	56946	paclitaxel		21 24	15.1% 17.3%	0.625	0.059
1 2	4179	etoposide		18 15	12.9% 10.8%	0.578	0.067
1 2	253337	bevacizumab		17 30	12.2% 21.6%	0.038	0.251
1 2	11202	vincristine		13 10	9.4% 7.2%	0.514	0.078
1 2	1547545	pembrolizumab		10 10	7.2% 7.2%	1	<0.001
1 2	1597876	nivolumab		10 10	7.2% 7.2%	1	<0.001
1 2	1721560	osimertinib		10 10	7.2% 7.2%	1	<0.001
1 2	2555	cisplatin		16 19	11.5% 13.7%	0.588	0.065
1 2	72962	docetaxel		10 12	7.2% 8.6%	0.657	0.053
1 2	337525	erlotinib		14 22	10.1% 15.8%	0.153	0.172
1 2	1430438	afatinib		10 10	7.2% 7.2%	1	<0.001
1 2	1727455	alectinib		10 10	7.2% 7.2%	1	<0.001
1 2	328134	gefitinib		10 10	7.2% 7.2%	1	<0.001
1 2	6851	methotrexate		28 25	20.1% 18.0%	0.647	0.055
1 2	68446	pemetrexed		23 32	16.5% 23.0%	0.175	0.163
1 2	3041	cytarabine		14 10	10.1% 7.2%	0.393	0.103
1 2	968804	Cytarabine liposome (deprecated 2020)		10 10	7.2% 7.2%	1	<0.001

1 2	10473	thiotepa		10 10	7.2% 7.2%	1	<0.001
Genomic							
Cohort			Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
1 2	3236	EGFR		10 10	7.2% 7.2%	1	<0.001
1 2	427	ALK		10 10	7.2% 7.2%	1	<0.001
1 2	7029	MET MET proto-oncogene, receptor tyrosine kinase		10 0	7.2% 0%	0.001	0.394
1 2	11998	TP53		10 10	7.2% 7.2%	1	<0.001
1 2	6407	KRAS		10 10	7.2% 7.2%	1	<0.001

Graphic 2 Analysis of outcomes (risk of death) performed on the cohorts after propensity score matching.

1 Death

Risk analysis

Cohort		Patients in cohort	Patients with outcome	Risk
1	QT IT Lung	139	102	0.734
2	without QTIT lung	139	82	0.590

		95% CI	z	p
Risk Difference	0.144	(0.034, 0.254)	2.536	0.011
Risk Ratio	1.244	(1.048, 1.476)	N/A	N/A
Odds Ratio	1.916	(1.156, 3.177)	N/A	N/A

Graphic 6. Sunburst Diagram (treatment pathway among cohort 1)