ANTICANCER RESEARCH *41*: 5333-5342 (2021)
doi:10.21873/anticanres.15346

Review

The Role of Immune Checkpoint Inhibitors in Leptomeningeal Disease: A Systematic Review

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Abstract. *Background/Aim: Leptomeningeal disease (LMD) is a debilitating complication of advanced malignancies. Immune-checkpoint inhibitors (ICIs) may alter disease course. We analyzed the role and toxicity of ICIs in LMD. Materials and Methods: We systematically reviewed the literature reporting on outcome data of patients with LMD treated with ICIs. Results: We included 14 studies encompassing 61 patients. Lung-cancer (44.3%), breast-cancer (27.9%), and melanoma (23.0%) were the most frequent primary tumors. Median duration of ICI-treatment was 7-months (range=0.5-58.0): pembrolizumab (49.2%), nivolumab (32.8%), ipilimumab (18.0%). Radiological responses included complete response (33.3%), partial response (12.5%), stable disease (33.3%), progressive disease (20.8%). Twenty-two patients developed ICI-related adverse-events, mild (100%) and/or severe (15.6%). Median progression-free and overall survival were 5.1 and 6.3 months, and 12-month survival was 32.1%. Survival correlated with ICI agents (p=0.042), but not with primary tumors (p=0.144). Patients receiving concurrent steroids showed worse survival (p=0.040). Conclusion: ICI therapy is well-tolerated in patients with LMD, but concurrent steroids may worsen survival.*

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Key Words: Brain metastasis, corticosteroids, immune checkpoint inhibitors, immunotherapy, leptomeningeal disease, review.

Leptomeningeal disease (LMD) occurs in 5-10% of oncological patients, most commonly from primary melanoma, lung, and breast neoplasms (1). LMD presents with new neurological impairments and focal/diffuse meningeal-enhancement at T1-contrast MRI, and is confirmed at cerebrospinal fluid (CSF) cytology (2). Available treatments include systemic/intrathecal chemotherapy, whole-brain/focal radiotherapy, and supportive-care; more recently, targeted-therapy and immunotherapy have been considered (3). The therapeutic goal remains palliation, with mean survival of 3-6 months (4, 5).

The immune system plays a major role in shaping the systemic response in neuro-oncology (6). Cancerous cells may elude the immune response by expressing immune-checkpoint ligands, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-L1), which suppress T-cell activation and proliferation (7). Immune-checkpoint inhibitors (ICIs) are novel agents directed at inhibiting these signals, enhancing immune recognition of tumors and T-cell response. ICIs have proven effective in brain metastases from melanoma, lung, and breast cancers, and clinical interest is expanding toward LMD (7-11).

Although ICIs represent an exciting development in neuro-oncology, their potential role in LMD remains unclear, with data derived only from few single-institution studies. We systematically reviewed the literature to summarize the use of ICIs in LMD, analyzing their role in improving quality-of-life and survival, and their toxicity profiles.

Materials and Methods

Literature search. A systematic review was performed upon the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (12). PubMed, EMBASE, Scopus, and Cochrane were searched from inception to March 23, 2021, operating the Boolean full-text search [(leptomeningeal disease OR leptomeningeal metastases OR leptomeningeal carcinomatosis OR carcinomatous meningitis OR neoplastic meningitis) AND (immunotherapy OR immune checkpoint inhibitors)]. Collected studies were exported to Mendeley; duplicates were removed. A second search was conducted on clinicaltrials.gov to identify ongoing clinical trials.

Study selection. Predetermined inclusion and exclusion criteria were set. Articles were included if they: 1) were retrospective/prospective studies including ≥1 patient diagnosed with LMD and treated with ICIs; 3) had available data on treatment outcomes and survival; 4) were written in English. Studies were excluded if they: 1) were reviews, animal, or laboratory studies; 2) lacked data on clinical/radiological responses or survival.

Two authors independently screened titles and abstracts of all identified papers and reviewed full texts of articles that met the inclusion criteria. A third author settled any disagreements. Eligible papers were included, and references screened to identify additional articles.

Data extraction. One reviewer extracted data from each article, then confirmed independently by two additional reviewers. Data included: author, study design, age, gender, primary tumor, brain metastases and treatment, PD-L1 expression, time-interval between primary tumor and LMD, LMD symptoms and radiological appearances, CSF-cytology, ICIs and duration of treatment, additional LMD treatment, Eastern Cooperative Oncology Group performance status (ECOG-PS) pre- and post-ICIs, LMD radiological response, LMD recurrence, progression-free survival (PFS), overall survival (OS), and survival status (13, 14).

LMD clinical – ECOG-PS post-ICI – and radiological responses were evaluated within the first 6-months of ICIs, as suggested in the iRANO statement (15). Radiological responses were assessed based on the RANO criteria modified for LMD, describing changes in the pathological brain and spine T1-contrast enhancement from baseline: complete-response (CR; no evidence of disease), partial-response (PR; >50% decrease in the summed product of orthogonal diameters of composite measurable nodules), stable-disease (SD; no change), progressive-disease (PD; >25% increase in the summed product of orthogonal diameters of composite measurable nodules or new sites of disease) (14).

Data synthesis and quality assessment. The primary outcomes of interest were patients' clinical outcomes, radiological responses, and survival. ICI-related adverse-events were also evaluated. Level of evidence was assessed using the 2011 Oxford Centre For Evidence-Based Medicine guidelines (16). Meta-analysis was precluded because most included studies had levels IV-V of evidence, and hazard-ratios could not be deducted. Risk of bias was independently appraised by two reviewers applying the Joanna Briggs Institute checklists for case-reports, case-series, and randomized controlled trials (17-19).

Statistical analysis. SPSS V.25 (IBM Corp, Armonk, New York) was used for statistical analysis. Continuous variables are presented as medians or means and ranges, categorical variables as frequencies and percentages. A two-sample weighted *t*-test was performed to assess differences between pre- and post-ICI ECOG-PS scores. Time-intervals between the start of ICI and LMD recurrence (PFS-curve) or death (OS-curve) were estimated using the Kaplan–Meier method; the survival analyses were conducted with the log-rank test. Two-sided p-value <0.05 was considered significant for all analyses.

Results

Study selection and overview. The search yielded 289 citations, of which 14 were included in the qualitative synthesis (Supplementary File 1). Nine were case-reports, four were retrospective case-series (including 32 patients), and one was a single-arm phase-II trial (including 20 patients); levels of evidence were V, IV, and IIb, respectively (Supplementary File 2) (8-11, 20-29). Critical appraisal resulted in low risk of bias for all included articles (Supplementary File 3).

Demographics, clinical and diagnostic characteristics. A total of 61 patients were analyzed (Supplementary File 2). Median age was 57 years with female predominance (63.9%) (Table I). Primary tumors were mostly lung-cancer (44.3%), breast-cancer (27.9%), and melanoma (23.0%). Thirty-seven patients (80.4%) presented with brain metastases, of which 31 (83.8%) treated with radiotherapy: 27 (73.0%) whole-brain radiotherapy (WBRT), four (10.8%) stereotactic radiosurgery (SRS). PD-L1 expression rates were evaluated from pathological specimens of nine patients with lung-cancer: high (expressed in ≥50% of tumor cells) in eight cases (88.9%), low (<50%) in one (11.1%).

Median time-interval between primary tumor and LMD was 10 months (range=0-48 months). The most common LMD symptoms were headache (42.1%), nausea/vomiting (23.7%), diplopia (23.7%), and facial-nerve palsy (10.5%). LMD diagnosis was obtained with MRI T1-contrast exams and/or CSF-cytology. Neuroimaging abnormalities included diffuse leptomeningeal-enhancement of the brain (96.7%) and/or spinal cord (3.2%), and simultaneous lumbar-nodular disease in two patients (3.2%). In two cases, normal MRI findings were reported (3.2%). CSF-cytology was obtained in 37 patients: positive in 32 (86.5%), negative in five (13.5%).

Management strategies, clinical and radiological responses, and adverse events. All 61 patients received ICIs for a median of seven months (range=0.5-58.0 months) (Table II).

The following agents were administered: pembrolizumab (Anti-PD1 monoclonal-antibody; Merck & Co., Kenilworth, NJ, USA) 2 mg/kg q3 weeks (49.2%); nivolumab (Anti-PD1 monoclonal-antibody; Bristol Myers Squibb, New York, NY, USA) 3 mg/kg q2 weeks (32.8%); ipilimumab (Anti-CTLA4 monoclonal-antibody; Bristol Myers Squibb, New York, NY, USA) 3 mg/kg q3 weeks (18.0%). Twenty-eight patients underwent concomitant treatments: WBRT (51.1%) and SRS (3.6%), corticosteroids (35.7%), dabrafenib/trametinib (BRAF-inhibitor/MEK-inhibitor; Novartis, Basel, Switzerland) (10.7%), systemic chemotherapy (3.6%) and intrathecal methotrexate (3.6%).

Median ECOG-PS scores were one both pre- and post-ICIs, and weighted means were not significantly different (p=0.176). Radiological responses were assessed in 24 patients: CR in eight (33.3%), PR in three (12.6%), SD in eight (33.3%), and PD in five (20.8%).

ICI-related adverse-events were described in 22/32 patients (68.7%) and reported using the "Common Terminology Criteria for Adverse Events, v5.0" (30). The most common were: grade-1, vomiting (27.3%), hyperglycemia (27.3%), constipation (22.7%) and fatigue (22.7%); grade-2, nausea and colitis (both 9.1%); grade-3, headache (13.6%).

Survival outcomes and analysis. LMD recurrence rate was 60.5%, and death occurred in 34 patients (55.7%). Median PFS and OS were 5.1 and 6.3 months, respectively (Table II). The 6-month PFS and OS rates were 46.1% and 50.9%, whereas the 12-month rates were 28.2% and 32.1%, respectively. The 6-month and 12-month survival rates stratified for primary tumor were 51.8% and 29.6% for lung-cancer, 30.0% and 10.0% for breast-cancer, 57.1% and 42.8% for melanoma, with median OS of 7.0, 5.2, and 9.1 months, respectively. The 6-month and 12-month survival rates stratified for ICIs were 50.0% and 40.9% for pembrolizumab, 55.0% and 25.0% for nivolumab, 45.4% and 27.3% for ipilimumab, with median OS of 5.9, 7.0, and 4.1 months, respectively. Median OS in patients receiving and not-receiving steroids concurrent to ICIs were 1.9 and 6.1 months, respectively.

No statistical difference in PFS was found based on the primary tumor (p=0.131), ICI agents (p=0.095), or concurrent use of steroids (p=0.92). No statistical difference in OS was found based on the primary tumor (p=0.144) (Figure 1), but OS was significantly lower in patients with concurrent use of steroids (p=0.040). Significant difference in OS was found based on ICI agents (p=0.042). Subgroup analyses showed significantly higher OS comparing pembrolizumab (median OS 35.0-months) with ipilimumab (median OS 4.1 months) (p=0.018) and nivolumab (median OS 33.5 months) with ipilimumab (p=0.031) for patients with melanoma, but not between pembrolizumab and nivolumab for patients with melanoma (p=0.808) and lung cancer (pembrolizumab median OS 12.5 months; nivolumab median OS 10.6 months) (p=0.342).

Table I. *Summary of demographics, clinical, and diagnostic characteristics of all pooled patients with leptomeningeal disease.*

Characteristics (no. of patients for whom information is available)	Value (among patients with available data)
Cohort size (no.)	61
Demographics	
Median age, range (years) (n=41)	57 (33-93)
Gender (female) (n=50)	39 (63.9%)
Primary tumor (n=61)	No. (%)
Lung	27 (44.3%)
Breast	17 (27.9%)
Melanoma	14 (23.0%)
Kidney	1 (1.6%)
Head & neck squamous cell carcinoma	1 (1.6%)
Ovary	1 (1.6%)
Secondary metastases (n=46)	No. (%)
Brain	37 (80.4%)
Lymph nodes	16 (34.8%)
Bone (Long bones, Spine, Skull base)	13 (28.3%)
Lung	6 (13.0%)
Liver	4 (8.7%)
Treatment brain metastases (n=37)	No. (%)
Radiation therapy	31 (83.8%)
Chemotherapy	5 (13.5%)
Surgery	4 (10.8%)
Intrathecal methotrexate	1 (2.7%)
PD-L1 expression (n=9)	No. (%)
High expression	8 (88.9%)
Low expression	1 (11.1%)
Time between primary tumor and LMD, months (range)	10.0 (0-48.0)
LMD presenting symptoms (n=38)	
No. (%)	
Headache	16 (42.1%)
Nausea/Vomit	9 (23.7%)
Diplopia	9 (23.7%)
Cranial nerve VII palsy	4 (10.5%)
Others	18 (47.4%)
Leptomeninges T1-contrast enhancement (n=61)	
No. (%)	
Brain diffuse	59 (96.7%)
Spine diffuse	2 (3.2%)
Lumbar nodule	2 (3.2%)
No contrast	2 (3.2%)
CSF cytology (n=37)	No. (%)
Positive	32 (86.5%)
Negative	5 (13.5%)

LMD: Leptomeningeal disease; CSF: cerebrospinal fluid.

Discussion

LMD is a devastating complication of advanced systemic malignancies, with uncertain optimal management and

Table II. *Summary of leptomeningeal disease treatment strategies and outcomes of all pooled patients.*

Characteristics (no. of patients for whom information is available)	Value (among patients with available data)
Cohort size (no.)	61
ICI therapy (n=61)	
No. (%)	
Pembrolizumab	30 (49.2%)
Nivolumab	20 (32.8%)
Ipilimumab	11 (18.0%)
Lung cancer (n=27)	
Nivolumab	18 (66.6%)
Pembrolizumab	9 (33.3%)
Melanoma (n=14)	
Ipilimumab	11 (78.6%)
Pembrolizumab	2 (14.3%)
Nivolumab	1 (7.1%)
Breast (n=17)	
Pembrolizumab	17 (100%)
Renal cell carcinoma (n=1)	
Nivolumab	1 (100%)
Head and neck squamous cell carcinoma (n=1)	
Pembrolizumab	1 (100%)
Ovarian cancer (n=1)	
Pembrolizumab	1 (100%)
Duration of ICI therapy (months), median (range) (n=41)	7.0 (0.5-58.7)
Concomitant LMD treatments (n=28)	No. (%)
Whole brain radiation therapy	16 (51.1%)
Stereotactic radiosurgery	1 (3.6%)
Corticosteroids	10 (35.7%)
BRAF inhibitor/MEK inhibitor	3 (10.7%)
Systemic chemotherapy	1 (3.6%)
Intrathecal methotrexate	1 (3.6%)
ECOG performance status	Median
Pre-ICI treatment (n=40)	1
Post-ICI treatment, first 6 months (n=42)	1
Radiological response, RANO criteria, first 6 months (n=24)	No. (%)
Complete response	8 (33.3%)
Partial response	3 (12.6%)
Stable disease	8 (33.3%)
Progression	5 (20.8%)
Patients with ICI-related adverse events (n=32)	22 (68.7%)
Type & Grade of ICI-related adverse events (CTCAE v5.0) (n=22)	
No. (%)	
G1: Vomiting	6 (27.3%)
Hyperglycemia	6 (27.3%)
Constipation	5 (22.7%)
Fatigue	5 (22.7%)
Diarrhea	2 (9.1%)
Rash	2 (9.1%)
G2: Nausea	2 (9.1%)
Colitis	2 (9.1%)
Pneumonitis	1 (4.5%)
G3: Headache	3 (13.6%)
Bone pain	1 (4.5%)
Lymphocytes/Platelet count decreased	1 (4.5%)
Muscle weakness lower limbs	1 (4.5%)
Inflammatory arthritis	1 (4.5%)
Strongyloides infection	1 (4.5%)
Recurrence of LMD (n=43)	26 (60.5%)
Outcome (months)	Median (range)
Progression-free survival (n=39)	5.1 (0.2-39.0)
Overall survival (n=53)	6.3 (0.5-58.7)
Status (n=61)	No. (%)
Alive	27 (44.3%)
Dead	34 (55.7%)

ICI: Immune checkpoint inhibitor; LMD: leptomeningeal disease; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group.

dismal survival (1, 2). This systematic review examined the role of ICIs in patients with LMD, noting their positive impact on quality-of-life and survival, coupled with low-rates of severe adverse-events.

The most common primary tumors were lung cancer, breast cancer, and melanoma, reflecting their overall prevalence among the general oncological population. These neoplasms represent the main oncological targets against which current ICIs have been proven effective, further confirming the promising role of ICIs in simultaneously modulating immunologic microenvironments of primary tumors and metastatic lesions (7, 31). The median time-interval from primary tumor to LMD was 10 months, largely lower than the 2-4 years range reported in previous series, probably because most patients presented with systemic metastases at the initial diagnosis (32, 33). In patients with brain metastases, resection and adjuvant radiotherapy of the surgical cavity have been demonstrated to increase risks of LMD by allowing tumor-cell spilling into the CSF (34, 35). In contrast, most of our pooled patients underwent radiotherapy alone for brain metastases preceding LMD. Our findings may corroborate a different pathological LMD mechanism, suggesting the direct trans-meningeal and intra-subarachnoid space spreading of cancer cells from adjacent parenchymal brain metastases, not adequately prevented by radiation (35).

Clinical evaluation with T1-contrast MRI and CSF-cytology assist the diagnostic workflow. Symptoms arise from the leptomeningeal dissemination of tumor cells, leading to CSF-flow obstruction with increased intracranial

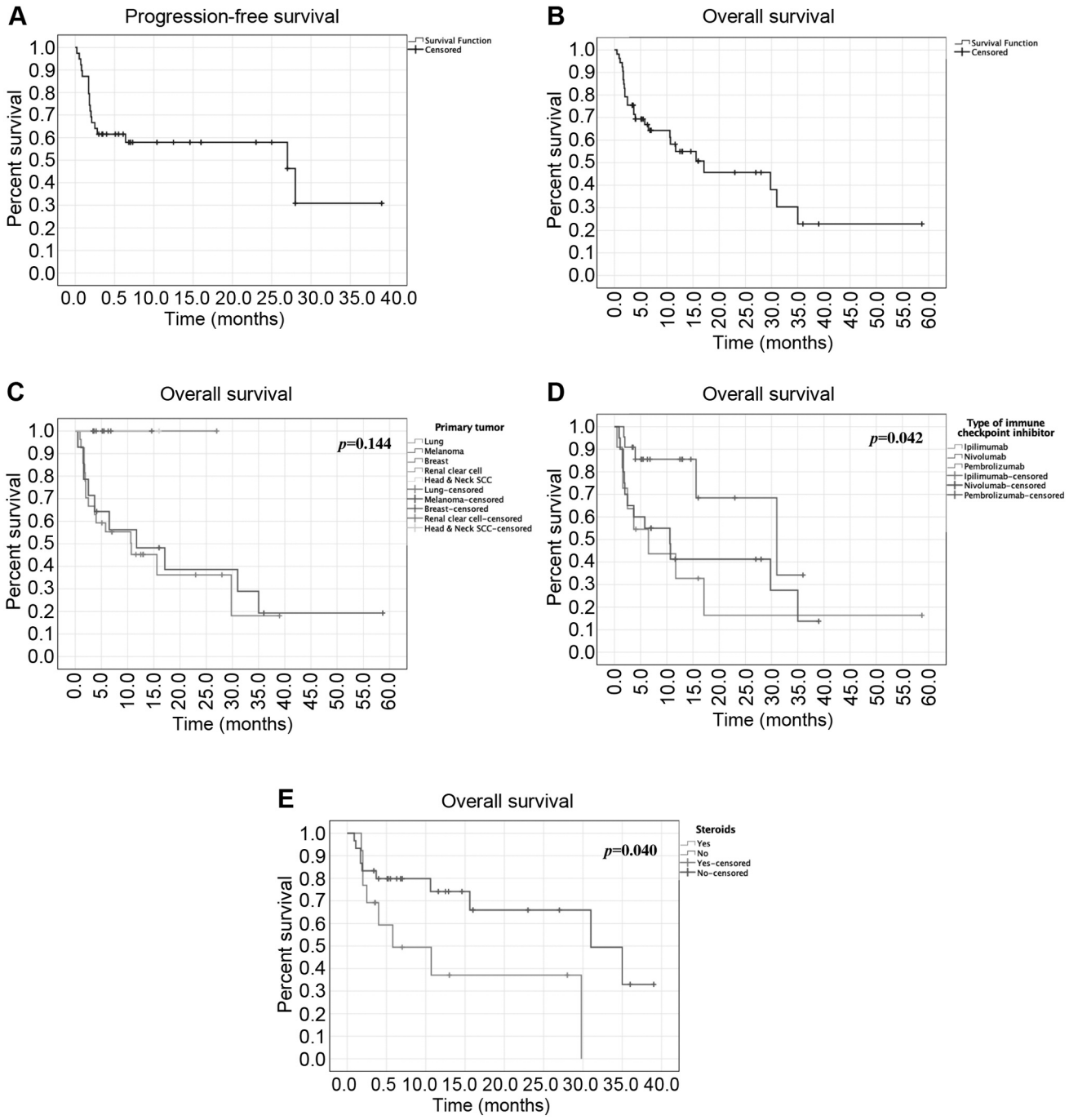

Figure 1. *Kaplan–Meier survival curves of patients with available individual data: A. Progression-free survival (n=39) and B. Overall survival (n=53) of the total pooled cohort; C. Overall survival (n=53) based on primary tumor; D. Overall survival (n=53) based on immune checkpoint inhibitor therapy; E. Overall survival (n=43) based on the use of steroids concurrent to immune checkpoint inhibitor use.*

pressure, and meningeal invasion (36). Accordingly, most of our pooled patients presented with headache, vomiting, and cranial-nerve palsies, but available data on hydrocephalus were scarce. In two singular cases, memory loss and auditory hallucinations were ascribed to the presence of temporo-insular LMD lesions (8, 21). Most LMD diagnoses were obtained after new symptom onset or upon routine follow-up surveillance in patients with metastatic disease. Most

patients exhibited diffuse brain and/or spinal cord MRI contrast-enhancement and confirmatory positive CSF-cytology. As estimated in up to 25% cases, we found few symptomatic patients presenting with normal MRI and positive-CSF cytology (3.2%), or negative CSF-cytology and pathological MRI (13.5%) (1). Hence, the clinical context remains key and needs to be integrated with imaging and CSF cytology for diagnosing LMD.

Challenges in the management of LMD relate to the poor clinical conditions of patients with systemic malignancies, with palliative therapies mostly intended to improve quality of life while avoiding toxicity. In our cohort, radiotherapy and corticosteroids were the most frequent treatments administered in concomitance with ICIs. Their preferred role derives from their ability to shrink tumors and facilitate CSF-flow, thus relieving symptoms and improving the distribution of intrathecal chemotherapeutics, which act against tumor cells within the CSF (37, 38). SRS is a feasible option in focal nodular-LMD, and, when adopted preoperatively, may also reduce the surgical risk of CSF cancerous spread from brain metastases (34, 39). However, no patients were deemed eligible for these SRS protocols across the collected studies. Despite showing promising results in LMD, molecular-therapies selectively treat neoplasms expressing specific target mutations, failing to be implemented in routine clinical practice (40). Indeed, only three of our pooled patients with melanoma (3/14, 21%) were eligible to receive concomitant BRAK/MEK inhibitors, corroborating the limits of targeted therapies and suggesting the superior feasibility of immunotherapeutic strategies.

Cancer cells may express immune-checkpoint molecules capable of suppressing protective T-cell responses; this has been also demonstrated for brain metastases (6, 31). ICIs promote anti-tumoral immune-modulatory responses by selectively preventing the interaction between these immune-suppressive molecules and cytotoxic T-cells in both primary and metastatic cancer sites. Several clinical-trials demonstrated the role of ICIs in controlling systemic and intracranial metastases from melanoma, lung, and breast malignancies (41-43). The immune response can also access the CSF compartment; thus ICIs may simultaneously treat primary tumors and leptomeningeal metastases, leading to the rapid lesion shrinkage with improvement of neurological symptoms and cognitive functioning (7, 9). Based on primary tumor origin, three ICIs/monoclonal antibodies have been validated for the treatment of LMD: ipilimumab acting against CTLA4; nivolumab and pembrolizumab targeting the PD-1/PD-L1 axis (9, 10, 28). In our cohort, ICIs correlated with prompt symptomatic relief and long-lasting positive functional status. In addition, at post-treatment radiological assessment, rates of stable disease (33.3%) and radiological responses (partial 12.6%; complete 33.3%) were higher than progression rates (20.9%). Due to LMD aggressive nature, coupled with the poor life expectancy of patients with systemic malignancies, treatments should primarily aim at preserving performance statuses and relieving debilitating symptoms. As opposed to the described limits of other therapies, ICIs appear to effectively prolong favorable functional status by contrasting LMD clinical and radiological progression.

In this review, the median OS (6.3 months), the 6-month (50.9%), and the 12-month survival rates (32.1%) were superior to those reported in previous large series of LMD (median OS 3 months; 6-month and 12-month survival rates of 28% and 10%, respectively) (44, 45). In those series, the extensive heterogeneity in primary tumors and treatment strategies accounted for the poor therapeutic response and survival. In contrast, the patients included in our analysis were selected based on their primary tumors for which ICIs had already proven to be effective. However, our findings were similar to survival obtained from previous studies selectively analyzing the role of radiotherapy or targeted-therapies in LMD (46, 47). In LMD, ICIs may improve survival on par with the other recommended treatments, but the poor baseline clinical status of affected patients likely limits their therapeutic efficacy.

Previous series described better survival of patients with LMD from breast cancer compared to melanoma and lung cancers, with approximate median OS of 4.5, 4.0, and 3.1 months respectively (4, 5, 28). In our cohort, we found superior median OS in patients with LMD from melanoma (9.1 months) compared to lung (7.0 months) and breast (5.2 months) cancers, but differences were not significant. Our findings may reflect the superior activity of single-agent checkpoint blockade in primary and metastatic melanomas and/or lung-cancers when compared to breast-cancers, which demonstrate better responses only with multiple ICI agents or multimodal adjuvant treatments (48-50). We noted significant differences in survival based on ICIs, regardless of primary tumors. Nivolumab yielded optimal median OS (7.0 months) and 6-month survival (55.0%), but pembrolizumab showed higher 12-month survival (40.9%). These differences were likely attributed to the large heterogeneity in tumor origins. Recent clinical-trials demonstrated that pembrolizumab and nivolumab significantly prolonged OS in patients with advanced melanoma when compared with ipilimumab (51, 52). Similarly, our subgroup analysis returned statistically higher OS in pembrolizumab and nivolumab treatments over ipilimumab for LMD originating from melanoma. We also found no significant difference in OS between nivolumab and pembrolizumab treatments for melanoma and lung cancers, as per previous studies describing their interchangeable role in the treatment of these neoplasms (53-55). Our findings likely relate to the suggested connections between immune microenvironments of primary tumors and LMD. They further support the feasibility of extending the clinical

applicability of ICIs, currently available mostly for primary tumors, to treat concomitant LMD.

As described in experimental models, steroids significantly reduce circulating T-cells and increase PD-1 expression, hampering anti-tumoral immune responses and ICIs' efficacy (56, 57). Steroids showed a detrimental effect on the survival of patients with brain metastases undergoing ICI therapy (58, 59). Brastianos *et al*. (9) reported worse OS in patients with LMD receiving steroids concurrent to pembrolizumab (2.4 months) compared to the non-steroid group (5.1 months), but differences were not significant (p=0.32). In our study, we found a significant correlation between OS and steroids use (p=0.040), with median OS of 1.9 and 6.1 months for steroid and non-steroid groups, respectively. ICIs and steroids independently provide symptomatic relief in patients with LMD, but their combination may negatively affect survival. Their deleterious impact on survival may be also connected to the likely worse burden of disease in patients who receive steroids for palliation. Our findings may suggest avoiding steroids in patients undergoing ICI therapy for LMD, but further prospective studies are required to better define their combined role, especially in patients with significant disease burden.

Patients with LMD are often considered too frail for aggressive treatments, and toxicity profiles should be evaluated first. In our cohort, we found a 68.7% rate of ICI-related adverse events, mostly mild, self-limited and with a low-impact on quality of life. Contrarily, mild radiotherapy adverse events (hair loss and skin reactions) occur in approximately 100% of patients, posing a significant cosmetic burden and affecting quality of life (3, 37). Severe ICI-related adverse-events (headache, bone marrow depression) were reported in 5 patients (15.6%) but were successfully treated with temporary ICI discontinuation and/or addition of steroids (8, 9, 24). Of note, the use of steroids for mitigating ICI-related adverse events has not been correlated with a negative impact on survival (59). In comparison, severe radiotherapy adverse events (neuroaxis toxicity, bone marrow depression) and intrathecal-chemotherapy adverse events (chemical and aseptic meningitis) often require hospitalization with surgery and/or prolonged antibiotic courses (37). Overall, rates and severities of our pooled adverse events were comparable with those of patients with primary and metastatic tumors undergoing ICIs (60). However, while recent studies reported incidences of fatal ICI-related adverse events ranging 0.3-13%, ICIs caused no life threatening side effects in our cohort, also showing better toxicity profiles than radiotherapy and intrathecal-chemotherapy (2, 40, 60).

Limitations. Our study has several limitations. Most included studies were case reports and retrospective case series, subjected to publication and selection biases. The only clinical trial was single-arm and open-label, not comparing ICIs' efficacy and toxicity profiles to other available treatments. The poor level-of-evidence of included studies precluded a meta-analysis and challenged the statistical power of this study. Some patient-level data could not be extracted in five studies, limiting our sample size and pooled analysis (9-11, 28, 29).

Conclusion

LMD is a serious late-stage complication of systemic malignancies with dismal prognoses. ICIs appear to be safe and effective in patients with LMD, improving survival while maintaining favorable quality of life. The concurrent use of steroids correlates with worse survival. Future randomized controlled trials are required to further assess the ICIs' role in the multimodal management of LMD, analyze their combined effect with steroids, and compare their efficacy to novel targeted therapies.

Supplementary Material

Available at: https://www.dropbox.com/sh/ktmmfizdxqjs585/AAChVN0ltD10B7PVzGfHogKMa?dl=0

Conflicts of Interest

The Authors have no relevant financial or non-financial interests to disclose.

Authors' Contributions

Paolo Palmisciano: Conceptualization, Methodology, Data analysis, Writing – Original draft preparation; Ali S. Haider: Resources, Writing – Reviewing and Editing; Chibueze D. Nwagwu: Resources, Writing – Reviewing and Editing; Waseem Wahood: Data analysis, Writing – Reviewing and Editing; Kenny Yu: Resources, Writing – Reviewing and Editing; Chibawayne I. Ene: Resources, Writing – Reviewing and Editing; Barbara J. O'Brien: Resources, Writing – Reviewing and Editing; Salah G. Aoun: Statistical analysis, Writing – Reviewing and Editing; Aaron A. Cohen-Gadol: Resources, Writing – Reviewing and Editing; Tarek Y. El Ahmadieh: Methodology, Resources, Writing – Reviewing and Editing, Supervision.

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Received August 21, 2021
Revised September 3, 2021
Accepted September 6, 2021