

BRIEF REPORT



Increased occurrence of status epilepticus in patients with brain metastases and checkpoint inhibition

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ABSTRACT

Integration of immune checkpoint inhibitors (ICIs) has improved the efficacy of treatment regimens for various cancers. The array of potential side effects keeps evolving and includes neurological complications. An increased risk of seizures and status epilepticus (SE) has been discussed and appears likely. In this report, we present clinical data from brain metastases patients undergoing ICI treatment revealing, for what we believe is the first time, SE as a serious adverse effect of ICI treatment. In our cohort of 3202 patients with brain metastases, we observed an increasing incidence of SE since the approval of ICIs in 2014 (16 patients in 2008–2013 vs. 36 patients in 2014–2019). Almost half of the patients treated in 2014–2019 received ICIs during the course of their disease, and in more than 80% of cases last dose of ICIs was given less than 30 days before SE. These findings suggest that ICIs may lead to an increased rate of SE in patients with brain metastases. Additional mechanistic research and prospective trials are necessary to elucidate the pathomechanism causing SE in patients treated with ICIs.

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Introduction

Status epilepticus (SE) is a medical emergency associated with a high mortality rate. About 7% of SE cases are caused by brain tumors or metastases.^{1,2} Several studies indicate that SE related to brain tumors is associated with higher mortality than non-tumor-related SE.^{1,3} New therapeutic options for brain tumors and metastases improve tumor-related outcomes. However, neurological side effects should be closely monitored.

The introduction of immune checkpoint inhibitors (ICIs) is a milestone in tumor therapy and has improved the efficacy of treatment regimens across various cancers. ICIs enhance anti-tumor activity of the immune system by inhibiting immune control points: programmed death-1 (PD-1: pembrolizumab, nivolumab and cemiplimab), programmed death ligand-1 (PD-L1: atezolizumab, durvalumab and avelumab) and cytotoxic T-lymphocyte antigen-4 (CTLA-4: ipilimumab).⁴ Several phase III trials have demonstrated efficacy in tumor treatment with an overall good level of tolerability; however, neurological immune-related adverse events may also occur.^{5,6} With increased use, rare but potentially serious adverse events will start occurring more frequently. In the past, a greater risk of seizures and SE has been proposed during treatment with ICIs. This side effect may be caused by an increased activation of the immune system or an increased inflammatory reaction.^{7,8}

An association between therapy with ICIs and an increased rate of SE has yet to be shown. In this report, we present clinical data

from patients with brain metastases undergoing ICI treatment that reveals SE as a serious adverse effect of ICI treatment.

Materials and methods

We investigated whether therapy with ICIs increases the risk for SE in patients with brain metastases and which characteristics were shown by patients belonging to this group. Therefore, we reviewed the medical records of all adult patients (age ≥ 18 years) treated for brain metastases using the hospital information system between January 2008 and December 2019. The University Hospital Frankfurt offers a full range of neurological care services with expertise in neuro-oncology, epileptology and intensive care medicine. The detailed evaluation of all SE patients is part of a study on SE outcomes.⁹

This retrospective cohort study was approved by the Institutional Review Board of the University Cancer Center (UCT) and the Ethical Committee at the University Hospital Frankfurt (project-number: SNO-13-2019). Informed consent was not required due to the deidentified nature of the data. For secured diagnosis of SE, patients needed at least one EEG classified as SE by a physician specialized in EEG diagnostics or an unequivocal clinical event. The definition and classification of SE was adopted based on the latest definitions proposed by the International League Against Epilepsy.¹⁰

Data on demographics, clinical diagnosis, tumor etiology and treatment, semiology and history of seizures or SE, use of anticonvulsants, total length of stay in hospital, and mortality were systematically collected in all patients. GraphPad Prism 8.0.2 and R version 3.5.2 was used for all statistical analyses. Chi-square test, Fisher's exact test and Gehan-Breslow-Wilcoxon test were used to analyze the collected data. *P* values were two-sided at a 5%-level of statistical significance.

Results

During the observation period, 3202 patients were identified that suffered from brain metastases, and 935 of these patients presented with neurological symptoms to the department of neurology. Among this population, we could confirm 52 cases of SE (CONSORT flow diagram Figure 1).

We observed an increasing incidence of SE since the approval of ICIs in 2014 (Figure 2a). The overall number of inpatients with brain metastases at our center had remained fairly constant over a six-year evaluation period before (471 patients in 2008–2013; Figure 2b) and after (464 patients in 2014–2019; Figure 2b) the introduction of ICIs. However, while the frequency of brain metastases patients with SE without ICI treatment has increased only slightly (16 patients in 2008–2013 vs. 19 patients in 2014–2019; Figure 2c), the overall frequency of SE at our center has increased significantly since the

approval and regular employment of ICIs in 2014 (36 patients in 2014–2019; $p < 0.01$; Figure 2c).

The mean age of patients suffering from SE associated with ICI treatment was 57.7 years ($n = 17$, median: 58 years; range: 40–71 years; female: 41.2%, $n = 7$). Patients' characteristics are shown in Tables 1 and 2. Primary cancer entities included melanoma ($n = 13$), lung cancer ($n = 3$), and bladder cancer ($n = 1$). Although most patients in the checkpoint-group suffered from metastasized melanoma, the main primary cancer in the non-ICI-group was lung cancer. Most patients ($n = 10$) received anti-PD-1/PD-L1 monotherapy with nivolumab, ipilimumab or pembrolizumab, whereas seven patients were treated with a combination of ipilimumab and nivolumab or pembrolizumab. The last dose of ICIs was given less than 30 days before onset of SE in 82% of patients [$n = 14$; median: 23.5 days, range: 2–325 days (interquartile range: 5.5–29.5 days)]. In total, 76.4% ($n = 13$) of the ICI patients had refractory SE. For comparison, only 17.1% ($p = .01$) of the patients in the non-ICI group had refractory SE. During the course of status therapy, 88.2% ($n = 15$) of the patients stopped ICI therapy. Beyond the discontinuation of ICI therapy, 82.4% of the patients were treated with steroids due to its anti-inflammatory and anti-edematous effect. Besides being administered a benzodiazepine (88.2%), 70.2% of patients received levetiracetam as the most common anticonvulsant. An average of 3.2 anticonvulsants were needed to terminate the SE. Comparing mortality across both cohorts, the Kaplan-Meier curve suggests a trend toward higher mortality in patients treated with ICIs, although this

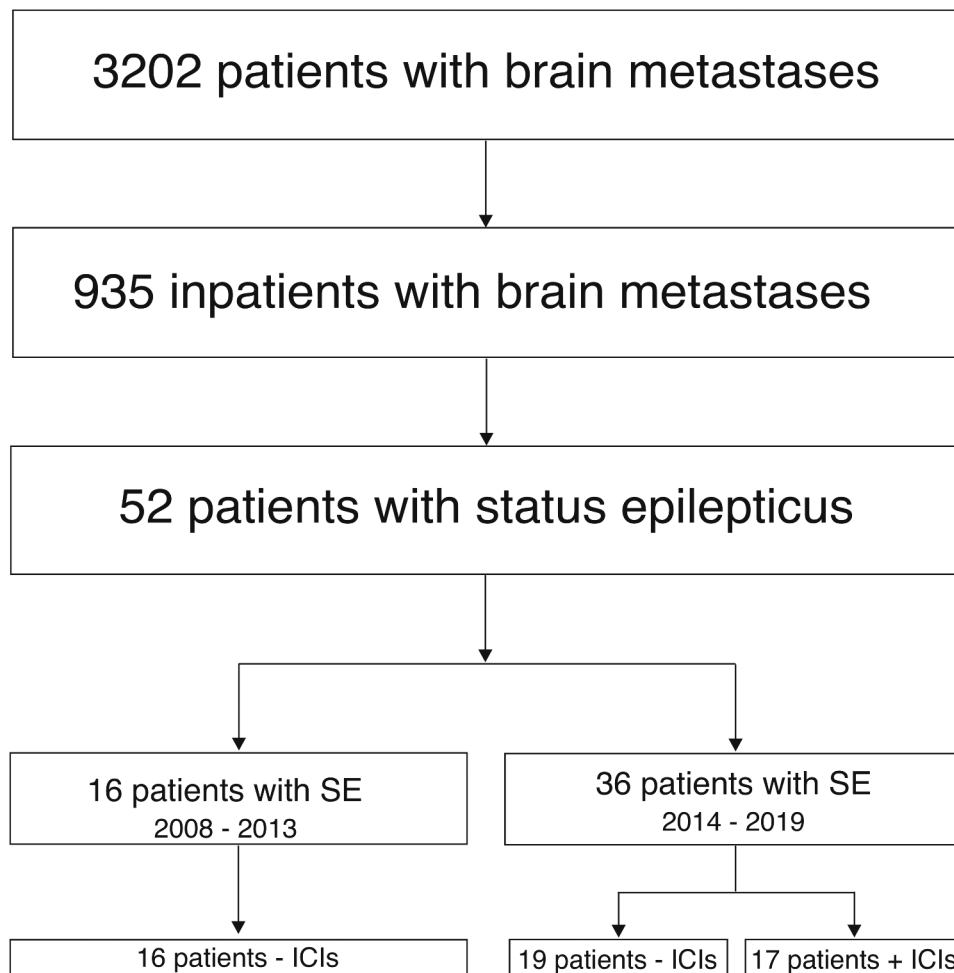


Figure 1. CONSORT flow diagram of study inclusion (“+ ICI” with and “- ICI” without checkpoint inhibitor treatment).

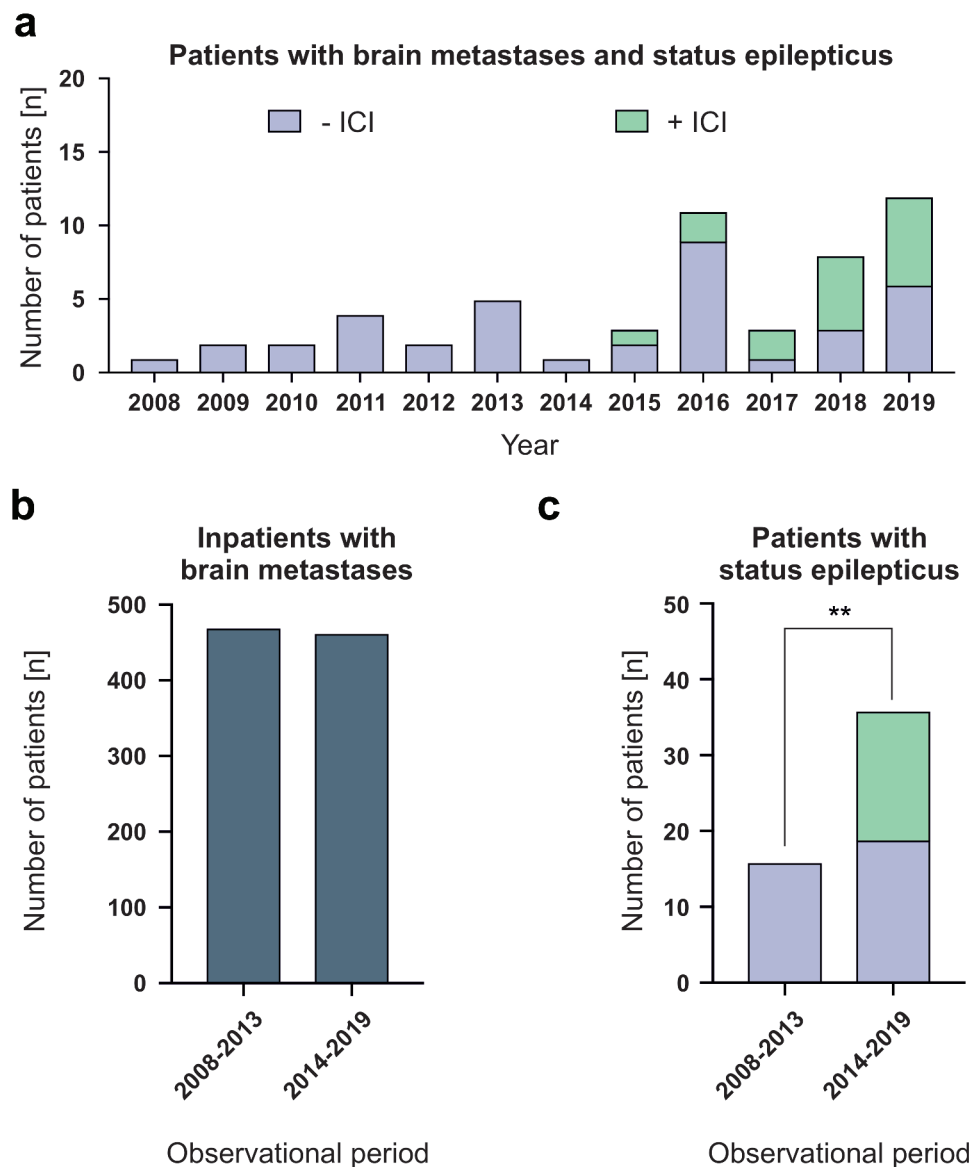


Figure 2. Increasing number of patients with status epilepticus in conjunction with immune checkpoint inhibitor therapy. (a) Annual number of patients with brain metastases, status epilepticus (SE), without (-ICI) or with (+ICI) immune checkpoint inhibitor (ICI) therapy. (b) Total number of inpatients at the Neurology Clinic with brain metastases and neurological deficits in the observation period. (c) Absolute number of patients with brain metastases, SE, and +/- therapy with ICIs in the 10 years of observation (Chi-Square-Test, p -value in relation to the number of intreated patients as shown in B. ** = $p < .01$)

difference was not significant. The 30-day mortality rates were 64.7% in SE patients with ICI treatment and 34.3% in SE patients without ICI treatment ($p = .09$; median survival time with ICI therapy 26 days vs. 60 days without ICI therapy; [Figure 3](#)).

Discussion

Our results demonstrate a significantly elevated risk of SE in patients with brain metastases under ICI treatment. Although we cannot decipher the underlying mechanism at the current time, there is a notable link between the use of ICIs and the rising incidence of SE. Several mechanisms can be considered: (i) Increased immune cell infiltration may generate an inflammatory microenvironment with increased perilesional edema and/or release of proconvulsive cytokines.^{7,8,11} Furthermore, (ii) epileptic seizures and SE may be caused by autoimmune encephalitis mediated by neuronal autoantibodies.^{12,13} This would offer an explanation for the

significantly increased rate of refractory status epilepticus in the checkpoint group and as well as for the comparatively poor response of ICI-associated SE to standard therapy with anti-seizure drugs. However, as observed in our cohort, ICI-associated SE responds relatively well to treatment with steroids or the discontinuation of ICI therapy. This is of particular importance since the occurrence of SE was associated with increased mortality in the group of patients treated with ICIs. Although this effect was not statistically significant, probably due to the small sample size, a connection can nevertheless be assumed here. It is important to consider inherent limitations associated with a noncontrolled study design and retrospective review format. The SE cases reported here occurred in a heterogeneous population of varying ages and comorbidities and showed different severity levels of SE. Patients were treated with different strategies that might influence the outcome of SE as shown in several studies.¹⁴⁻¹⁶ Individual cases may therefore respond differently to treatments and have contrasting prognoses.

Table 1. Characteristics of status epilepticus patients for the overall cohort and those with and without ICI treatment.

Patient characteristics	Feature	Overall	with immune checkpoint Inhibitor	without immune checkpoint Inhibitor
<i>N</i>		52	17	35
Age (year)		59.87	57.7	62
Sex (%)	Male	27 (52%)	10 (59%)	17 (49%)
	Female	25 (48%)	7 (41%)	18 (51%)
Entity	Melanoma (%)	17 (33%)	13 (76%)	4 (11%)
	Lung cancer (%)	18 (34%)	3 (18%)	15 (43%)
	Breast Cancer	4 (8%)	0 (0%)	4 (11%)
	Other entities*	13 (25%)	1 (6%)	12 (34%)
Tumor burden				
Number of brain metastases	1	20	4	16
	2–5	11	4	7
	>5	21	9	12
Number of affected organs (excluding brain)	1	22	8	14
	2	11	2	9
	>3	18	7	11
	Unknown	1		1
Previous therapy	Chemotherapy	36	10	26
	Local surgery of the origin cancer	31	10	21
	Brain surgery	12	4	8
	Radiation	20	6	14
	Brain Radiation	18	7	11
	– Stereotactic brain radiation	30	12	18
	– Whole brain radiation	9	2	7
	Checkpoint Inhibitors	19	19	0
	– Monotherapy	10	10	
	– Combination of 2 ICIs	7	7	
	Tyrosinkinase Inhibitors	5	5	0
	Unknown previous therapy	4	0	4
Refractory status epilepticus		19 (37%)	13 (76%)	6 (17%)

* includes colorectal cancer, bladder cancer, hepatic cancer, sarcoma, prostate cancer, cancer of unknown origin, renal cancer.

Table 2. Characteristics of status epilepticus patient for the overall cohort and for the time periods 2008–2013 and 2014–2019.

Patient characteristics	Feature	Overall	2008–2013	2014–2019
<i>N</i>		52	16	36
Age (year)		59.87	59.75	60.11
Sex (%)	Male	27 (52%)	8 (50%)	19 (53%)
	Female	25 (48%)	8 (50%)	17 (47%)
Entity	Melanoma (%)	17 (27%)	4 (25%)	13 (36%)
	Lung cancer (%)	18 (34%)	5 (31%)	13 (36%)
	Breast Cancer	4 (8%)	0	4 (11%)
	Other entities*	13 (25%)	7 (44%)	6 (17%)
Tumor burden				
Number of brain metastases	1	20	11	9
	2–5	11	0	11
	>5	21	5	16
Number of affected organs (excluding brain)	0–1	22	7	15
	2	11	5	6
	>3	18	3	15
	Unknown	1	1	0
Previous therapy	Chemotherapy	36	10	26
	Local surgery of the origin cancer	31	12	19
	Brain surgery	12	2	10
	Radiation	20	11	9
	Brain Radiation	39	14	25
	– Stereotactic brain radiation	30	12	18
	– Whole brain radiation	9	2	7
	Checkpoint Inhibitors	19	0	19
	– Monotherapy	10	0	10
	– Combination of 2 ICIs	7	0	7
	Tyrosinkinase Inhibitors	5	2	3
	Unknown previous therapy	4	2	2
Refractory status epilepticus		19 (37%)	5 (31%)	14 (39%)

* includes colorectal cancer, bladder cancer, hepatic cancer, sarcoma, prostate cancer, cancer of unknown origin, renal cancer.

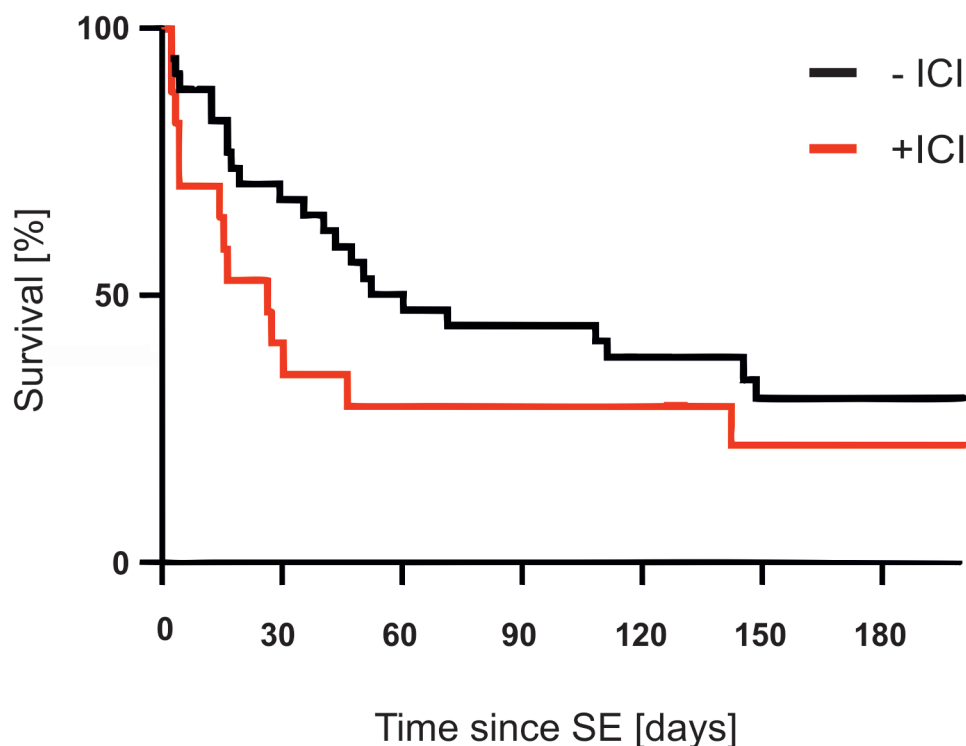


Figure 3. Survival of patients with an without immune checkpoint therapy after the status epilepticus. Kaplan-Meier curve of patients with brain metastases, status epilepticus and treated with or without immune checkpoint inhibitors. Median survival after status epilepticus was 26 days with ICI therapy and 60 days without ICI therapy.

Conclusion

Our results need to be interpreted with caution given the small sample size and the retrospective study design from a single center. However, since ICIs are increasingly employed, a further rise in the occurrence of SE in patients with brain metastases can be expected. We therefore recommend vigilance for SE in patients treated with ICIs, as this is a potentially life-limiting side effect of an otherwise effective therapy. Future mechanistic studies and prospective trials are needed to elucidate the mechanism of SE associated with ICIs.

Authors' contributions

HU, LMW and AS developed the idea for this study. HU, LMW, and AS collected the data. HU, FR, JPS and AS analyzed the data. HU, FR and AS interpreted the data. HU and MWR designed the figures. HU, LMW, MWR, JPS and AS wrote the manuscript. All authors read and approved the final manuscript.

List of Abbreviations

ICIs	immune checkpoint inhibitors
SE	status epilepticus
UCT	University Cancer Center

Ethical publication guidelines

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure of potential conflicts of interest

HU and LMW have nothing to disclose.

MWR reports research grants from UCB, outside the submitted work.

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