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Clinical Course of Neurologic Adverse Events Associated With Immune Checkpoint Inhibitors

Focus on Chronic Toxicities

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Abstract

Background and Objectives

The clinical course and the risk of chronicity of neurologic immune-related adverse events (n-irAEs) associated with immune checkpoint inhibitors (ICIs) are not well documented. This study aimed to characterize the clinical course of n-irAEs and assess the prevalence of chronic events.

Methods

This nationwide, multicenter, retrospective study included patients with n-irAEs identified at 7 Italian hospitals. The clinical course of n-irAEs was categorized into fulminant (if resulted in death within 12 weeks), monophasic (if resolved within 12 weeks), and chronic (if persisted beyond 12 weeks). Chronic n-irAEs were further subdivided into *active* (if there was indirect evidence of ongoing inflammation [i.e., required ongoing immunosuppression, relapsed on steroid tapering, or exhibited neurologic progression]) and *inactive* (if patients had neurologic sequelae without ongoing inflammation). Comparisons between groups and time-to-death analyses were performed.

Results

Sixty-six patients were included (median age: 69 years [IQR 62–75]; 53 [80%] men). n-irAEs involved the peripheral nervous system in 48 patients (73%), the central nervous system in 14 (21%), and both in 4 (6%). Twelve patients (18%) had a fulminant course, with the risk being significantly higher in those with concurrent myocarditis (OR 5.4; 95% CI [1.02–28.31]). Among 54 patients with a nonfulminant course, 23 (43%) had a monophasic n-irAE and 31 (57%) had a chronic n-irAE, of which 16 of 31 (52%) were chronic *active* (due to ongoing immunosuppression [69%], relapses at corticosteroid tapering [19%], or neurologic disease progression [12%]) and 15 of 31 (48%) were chronic *inactive*. In patients with chronic inactive n-irAEs, neurologic sequelae included cerebellar ataxia (33%), neuromuscular weakness (27%), visual loss (13%), sensory disturbances (13%), focal neurologic signs (7%), and cognitive impairment (7%). Compared with patients with monophasic events, those with chronic n-irAEs had a higher rate of severe neurologic disability at the last evaluation ($p < 0.01$), shorter survival ($p < 0.01$), and higher overall mortality ($p < 0.01$), primarily due to cancer progression.

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Glossary

CTCAE = Common Terminology Criteria for Adverse Events; **CTLA-4** = cytotoxic T-lymphocyte antigen 4; **FLAIR** = fluid-attenuated inversion recovery; **ICI** = immune checkpoint inhibitor; **IQR** = interquartile range; **irAE** = immune-related adverse event; **IVIGs** = IV immunoglobulins; **MG** = myasthenia gravis; **mRS** = modified Rankin Scale; **n-irAE** = neurologic immune-related adverse event; **OR** = odds ratios; **PD-1** = programmed death protein 1; **PLEX** = plasma exchange; **PNS** = paraneoplastic neurologic syndrome; **SITC** = Society for Immunotherapy of Cancer.

Discussion

More than half of the patients with n-irAEs who survived the acute phase developed a chronic condition. Patients with chronic n-irAEs were at higher risk of death, mainly due to cancer progression. Future studies are needed to further characterize chronic n-irAEs and identify optimal long-term management strategies.

Introduction

The advent of immune checkpoint inhibitors (ICIs) has dramatically changed the landscape of cancer treatment in the past 10 years. By blocking immune checkpoints, cell-surface molecules that act as downregulators of the immune system and include cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death protein 1 (PD-1), and its ligand (PD-L1), ICIs enhance endogenous antitumor responses.[1] However, ICIs also activate the immune system in a nonspecific manner, which underpins their unique profile of toxic effects, collectively named as immune-related adverse events (irAEs).[2] Neurologic irAEs (n-irAEs) occur in 1%–3% of patients treated with ICIs[3-5] and manifest along a wide clinical spectrum, which includes myositis, peripheral and cranial neuropathies, meningitis, and encephalitis as the commonest manifestations.[6,7] Despite their rarity, n-irAEs are clinically relevant because they are often severe and may be life-threatening. For instance, ICI-related myositis may associate with myocarditis, manifesting in a fulminant manner with rapidly fatal course despite ICI withdrawal and immunosuppression.[8] In addition, although most n-irAEs resolve with ICI discontinuation and initial corticosteroid treatment, thus manifesting with a "monophasic" course,[3,9] up to one-third of patients present neurologic sequelae and severe long-term disability.[10-12] The concept that organ dysfunction due to irAEs may persist long term after ICI discontinuation has been recently addressed by the Society for Immunotherapy of Cancer (SITC), which defined an irAE as *chronic* if it persists beyond 3 months of ICI discontinuation, due to permanent organ damage (*chronic inactive irAE*) or ongoing inflammation (*chronic active irAE*).[13] Endocrine toxicities—in which the hormone-secreting cells are irretrievably damaged or ablated by the inflammatory process—represent the most frequent and a paradigmatic example of chronic inactive irAEs.[11] Although n-irAEs have been reported among the most frequent nonendocrine chronic irAEs (19% in a recent systematic review),[14] a comprehensive assessment of the clinical course of n-irAEs is lacking and chronic n-irAEs have not been well characterized. In this article, we studied the prevalence of fulminant, monophasic, and chronic n-irAEs in a nationwide cohort and explored potential associations of the clinical course of n-irAEs with baseline features, neurologic phenotypes, and outcomes.

Methods

Study Design and Patient Selection

In this multicenter retrospective cohort study, we enrolled consecutive patients with n-irAEs at 7 tertiary centers in Italy (Bologna, Pavia, Udine, Florence, Rome, Verona, and Vicenza) between January 1, 2016, and October 1, 2023. In all cases, the diagnostic workup was conducted by the local treating physician. The diagnosis of n-irAEs was based on the temporal relationship with ICI administration (i.e., within 12 months of the last ICI infusion) and the exclusion of other potential etiologies (including cancer dissemination, metabolic disturbances, neuroinfections, or other chemotherapies-related toxicities) by a comprehensive diagnostic workup, in accordance with the consensus definition paper.[15]

We collected demographic, oncological, clinical, and diagnostic data (including blood and CSF analysis, nerve conduction studies, EMG, EEG, MRI) and recorded the modalities in which the n-irAE was managed (whether the ICI was discontinued; doses and timing of eventual immunosuppressive or immunomodulatory treatment). We assessed the severity of n-irAEs using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which ranges from 1 (mild symptoms) to 5 (death caused by the adverse event).[16] Neurologic disability was evaluated using the modified Rankin Scale (mRS) score[17] (retrospectively assessed before ICI initiation, at symptom nadir, and at the last available neurologic evaluation) and considered as severe when the mRS score was ≥3. The chart was assessed for data homogeneity and completeness by 2 authors (S.R., M.G.); in case of missing or incomplete data, they were requested to the treating physician. Neurologic phenotypes were classified according to the consensus definition.[15]

We distinguished 4 categories of clinical courses: (1) *fulminant,* if the patient died as a consequence of the neurotoxicity within 3 months of n-irAE onset; (2) *monophasic*, if the n-irAE resolved within 3 months from ICI discontinuation, without further need for immunosuppressant and no evidence of relapses after immunosuppressant discontinuation; (3) *chronic active*, if symptoms persisted beyond 3 months of ICI discontinuation with indirect evidence of persisting inflammation (i.e., relapse at corticosteroid reduction, need for ongoing immunosuppression, or neurologic disease progression during immune-active treatment); (4) *chronic inactive*, if the patient had neurologic sequelae beyond 3 months of ICI discontinuation, without indirect evidence of persisting inflammation. The limit of 3 months from the last ICI administration to define a n-irAE as chronic and the distinction between chronic active and inactive were established in accordance with the SITC consensus definition.[13]

The presence of concurrent non-neurologic irAEs was recorded, and patients were categorized as having (1) no concurrent non-neurologic irAEs, (2) concurrent myocarditis, or (3) concurrent non-neurologic irAEs different from myocarditis. Myocarditis was separated from other non-neurologic irAEs because of its different prognostic and biological characteristics.[5,18] The follow-up time was defined as the time from n-irAE onset to death (if caused by the n-irAE) or to the last available neurologic evaluation.

The presence of antibodies to intracellular/surface or glial antigens, AChR, and MuSK was assessed, when clinically indicated, at local laboratories. Patients fulfilling the definition of probable or definite paraneoplastic neurologic syndromes (PNSs), according to the updated criteria from Graus et al.,[19] were referred to as having a paraneoplastic-like n-irAE.

We excluded from the analysis (1) patients who were lost to follow-up before 3 months from n-irAE onset; (2) patients who died within 3 months from n-irAE onset for causes other than the neurologic toxicity (e.g., cancer progression); and (3) patients with incomplete information concerning demographic data, clinical aspects, neurologic disability, treatments, and prognosis.

Statistical Analysis

Continuous descriptive data were presented using median and interquartile range (IQR) and categorical variables using absolute number and percentage. Two-group comparisons were assessed using Mann-Whitney *U* tests for continuous variables and categorical comparisons with the chi-squared statistic (or the Fisher exact test when required). Comparisons between more than 2 groups were undertaken using the Kruskal-Wallis test.

Univariable analyses were performed to examine association among the variables and the 4 clinical courses. In addition, these associations were examined also between fulminant and all the other clinical course groups taken together (dichotomous outcome). The multivariable analysis for the association of prognostic factors with the dichotomous outcome was performed using logistic regression. Odds ratios (ORs) and 95% CIs were reported.

Time to death was analyzed with the Kaplan-Meier survival curve using the log-rank test to compare clinical courses. *p* values were 2-tailed, and for all analyses, $p < 0.05$ was considered significant. Statistical analyses were performed using Stata version 16.2.

Ethics Statement

The study was approved by the institutional ethic committee (No. 20190026431). Written informed consent was obtained from included patients.

Data Availability

Anonymized data will be shared to any qualified investigator on reasonable request.

Results

Cohort Description

Sixty-six patients were included in the study (median age: 69 years [IQR 62–75]; 80% male, Figure 1, Table 1). Underlying malignancies included non–small-cell lung cancer (32%), melanoma (29%), urological malignancies (17%), or other cancers (23%), and the offending ICIs were PD-1 inhibitors (67%), PD-L1 inhibitors (24%), CTLA-4 inhibitors (3%), or a combination of PD-1 and CTLA-4 inhibitors (6%; Table 1). None of the included patients had a pre-existing paraneoplastic neurologic syndrome nor a history of neurologic autoimmunity. Neurologic symptoms occurred after a median of 8.7 weeks (IQR 4–26.3) and 3 cycles (IQR 2–8) from the first ICI dose. n-irAEs involved the peripheral nervous system (48/66, 73%), the CNS (14/66, 21%), or both (4/66, 6%; Figure 1).

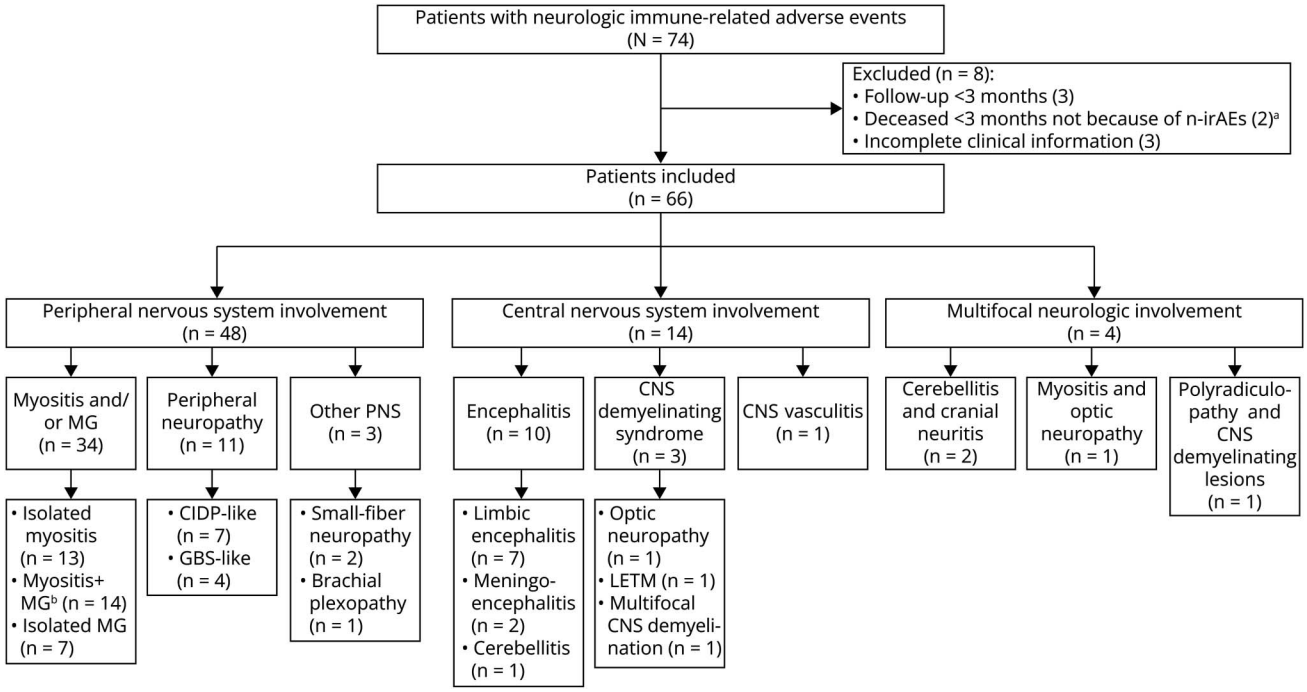
Anti-neuronal/glial antibodies were positive in 10 of 40 tested patients (25%) (anti-Hu, 2; anti-Ma2, 2; anti-Hu plus anti-CV2, 1; anti-AQP4, 1; anti-GFAP, 1; anti-Ri, 1; anti-SOX1, 1; anti-neuronal intermediate filament, 1). Anti-AChR antibodies were detected in 13 of 32 tested patients (7 with myasthenia gravis [MG], 6 with MG and myositis).

Eleven patients (17%) fulfilled the criteria for definite or probable PNS (limbic encephalitis, 6 patients; rapidly progressive cerebellar syndrome, 3 patients; peripheral neuropathies, 2 patients). Concurrent non-neurologic irAEs were recorded in 29 patients (44%), and the most frequent was myocarditis (14 patients, 21%), always occurring in association with myositis and/or MG.

At nadir, the CTCAE grade was ≥3 in 45 of 66 patients (68%) and the median mRS score was 3 (IQR 2–6).

ICIs were withheld in all 66 patients (100%), and most of them received an immune-active treatment (63/66, 95%).

Figure 1 Flowchart of Patients With Neurologic Immune-Related Adverse Events Included in the Study and Their Clinical Phenotypes



[a]1 patient with melanoma and immune-related polyradiculoneuropathy who died 2 months after n-irAE onset because of intracerebral hemorrhage (bleeding of brain metastases); 1 patient with melanoma and immune-related cranial neuropathy (bilateral VII and VIII cranial nerve involvement) who died 2.5 months after n-irAE onset because of bowel obstruction. [b]In patients with myositis, the presence of myasthenic features was documented by decremental response to repetitive nerve stimulation (7 patients) or by clinical response to acetylcholinesterase inhibitors (7 patients). CIDP = chronic inflammatory demyelinating polyneuropathy; GBS = Guillain-Barrè syndrome; LETM = long-extensive transverse myelitis; MG = myasthenia gravis; n-irAE = neurologic immune-related adverse event; PNS = peripheral nervous system.

Steroids were administered as the first-line treatment in 61 patients (92%) and were the only immune-active medication in 37. Most of the patients received IV steroids (37/61, 60%) at a median starting dose of 175 mg/d of prednisone equivalent (IQR 75–1,000). Twenty-three patients (35%) received a nonsteroid immune-active treatment, including IV immunoglobulins (IVIGs, 19 patients), plasma exchange (PLEX, 4 patients), rituximab (2 patients), anakinra (1 patient), tocilizumab (1 patient), and eculizumab (1 patient). In most of the patients (21/23, 91%), nonsteroid immune-active treatment was administered as an escalation therapy after a nonsuccessful attempt with first-line steroids; 2 patients (3%) were primarily managed with IVIGs and/or PLEX. After a median follow-up period of 6.5 months (IQR 4–16), the median mRS score was 1 (IQR 0–3) and 25 patients (38%) had died, because of neurotoxicity (13/25), cancer progression (11/25), or other causes (COVID-19 pneumonia, 1/25).

Fulminant n-irAEs

Among the 13 patients who died because of the neurotoxicity, 12 (92%) died within 3 months of onset of neurologic symptoms and were, therefore, classified as having a fulminant course (12/66, 18%). All except 1 had a neuromuscular irAE: 4 MG/myositis (all with concurrent myocarditis), 4 myositis (3/4 with concurrent myocarditis), 2 MG (1 with concurrent myocarditis), and 1 GBS-like syndrome; the remaining patient had limbic encephalitis with anti-Ma2 antibodies (Figure 2, A and B).

Compared with the rest of the cohort, patients with a fulminant course were older ($p = 0.001$), had a shorter latency from ICI initiation to neurologic toxicity ($p = 0.010$), showed a higher neurologic disability at onset ($p < 0.001$), were more likely to receive IVIGs and/or PLEX ($p = 0.003$), and had more commonly concurrent myocarditis ($p = 0.001$). In the multivariate analysis, a higher risk of having a fulminant course was independently associated with concurrent myocarditis (OR = 5.4; 95% CI = 1.02–28.31). Additional data from the multivariate analysis are reported in eFigure 1.

Nonfulminant n-irAEs

Among the 54 patients with a nonfulminant course, 23 (43%) had a monophasic course and 31 (57%) had a chronic course, of which 16 of 31 (52%) were classified as chronic active and 15 of 31 (48%) as chronic inactive (Figure 3, Table 2). Patients with chronic active n-irAEs had myositis and/or MG (9 patients; Figure 2, C and D), peripheral neuropathy (4 patients), encephalitis (2 patients), and myelitis (1 patient). n-irAEs were considered as active because of ongoing immunosuppression (11/16, 69%), relapses at corticosteroid

Table 1 Demographics, Clinical Features, and Outcomes of the Entire Cohort of Patients With Neurologic Immune-Related Adverse Events

	All patients (n = 66)
Age, y	69 (62–75)
Sex, n (%)	
Male	53 (80.3)
Female	13 (19.7)
Tumor, n (%)	
NSCLC	21 (31.8)
Melanoma	19 (28.8)
Urological cancers	11 (16.7)
Other types of cancer[a]	15 (22.7)
ICI class, n (%)	
Anti–PD-1	44 (66.7)
Anti–PD-L1	16 (24.2)
Anti–CTLA-4	4 (6.1)
Combination therapy[b]	2 (3)
Neurologic involvement, n (%)	
PNS	48 (72.7)
CNS	14 (21.2)
Multifocal	4 (6.1)
Latency to n-irAE onset, wk	8.7 (4–26.3)
Symptom progression, n (%)	
Acute	28 (42.4)
Subacute	30 (45.5)
Insidious	8 (12.1)
Non-neurologic irAEs	29 (44)
Myocarditis	14 (21)
Other[c]	15 (23)
Neurologic disability, mRS score	
Clinical nadir	3 (2–5)
Last follow-up	1 (0–3)
CTCAE 5.0 (median), n (%)	3 (2–4)
Grade <3	21 (32)
Grade ≥3	45 (68)
Treatment scheme, n (%)	
ICI discontinuation	66 (100)
Immune-active treatments	63 (95.5)
No immune-active treatments	3 (4.5)
ICI rechallenge, n (%)	
Number	8 (12)
Latency from ICI discontinuation (mo)	3 (2.75–4)
Follow-up, mo	6.5 (4–16)
Deaths, n (%)	25 (37.9)
Due to n-irAE	13 (19.7)
Due to cancer progression	12 (18.2)

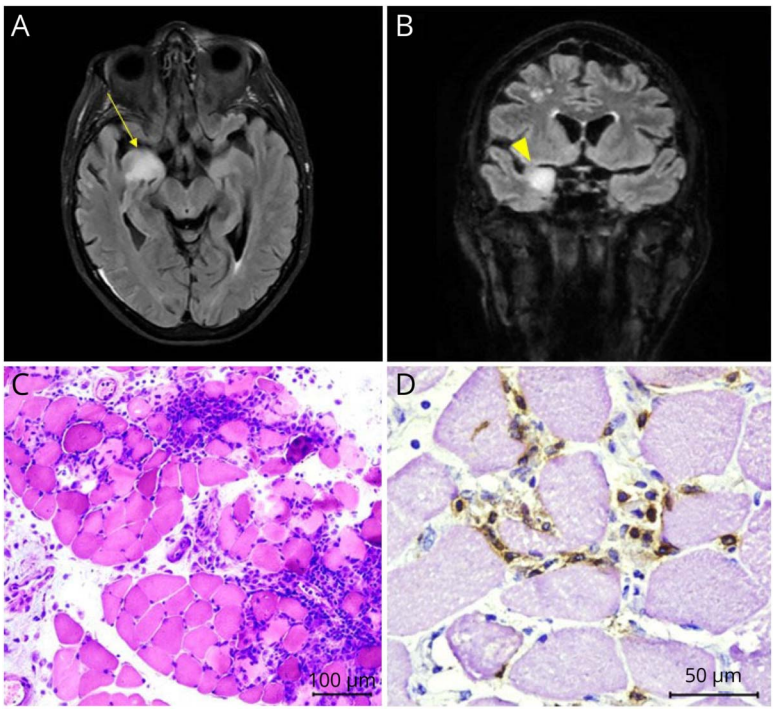
Abbreviations: CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; ICI = immune checkpoint inhibitor; n-irAE: neurologic immune-related adverse event; NSCLC = non–small-cell lung cancer; PD-1 = programmed death protein 1; PD-L1 = programmed death protein ligand 1.
Data are presented as number with percentage (%) or median with interquartile range variation (IQR).
[a] Other types of cancers included small-cell lung cancer (5 patients), Merkel cell carcinoma (3 patients), gastrointestinal cancers (6 patients), and hepatocellular carcinoma (1 patient).
[b] Combination therapy included anti–PD-1 plus anti–CLTA-4.
[c] Other non-neurologic irAEs included thyroiditis (8 patients), hepatitis (6 patients), dermatologic lesions (3 patients), pneumonitis (2 patients), and colitis (one patient).

tapering (3/16, 19%), or neurologic deterioration during immune-active treatment (2/16, 12%). At the last available neurologic evaluation (median follow-up time of 11 months [IQR 4.8–16.5]), all 16 patients (100%) with a chronic active n-irAE were still receiving an immune-active treatment, including steroids (14/16, 87%), IVIGs (6/16, 37%), rituximab (2/16, 12%), and eculizumab (1/16, 6%).

Among patients with chronic inactive n-irAEs, 4 had encephalitis, 4 had peripheral neuropathy, 2 had myositis (1 isolated myositis; 1 myositis and MG), 2 had CNS demyelinating syndromes, 1 had CNS vasculitis, and 2 had multifocal neurologic involvement (1 encephalitis and oculomotor nerve palsy; 1 myositis and unilateral optic neuritis). Neurologic sequelae included cerebellar ataxia (5 patients [33%]), neuromuscular weakness (4 patients [27%]), visual loss (2 patients [13%]), sensory disturbances (2 patients [13%]), focal neurologic signs (1 patient [7%]), and cognitive impairment (1 patient [7%]). Additional data about clinical phenotype and neurologic sequelae of patients with chronic inactive n-irAEs are reported in eTable 1.

Peripheral nervous system involvement was more frequent in patients with monophasic and chronic active n-irAEs (78% and 82%, respectively) compared with patients with chronic inactive n-irAEs (40%; $p = 0.044$) while CNS involvement was more frequent in patients with chronic inactive n-irAEs (47% vs 13% and 18% [monophasic and chronic active, respectively], $p = 0.04$) (Figure 3, Table 2). Concurrent non-

Figure 2 MRI of the Brain and Muscle Biopsy of 2 Patients With n-irAEs

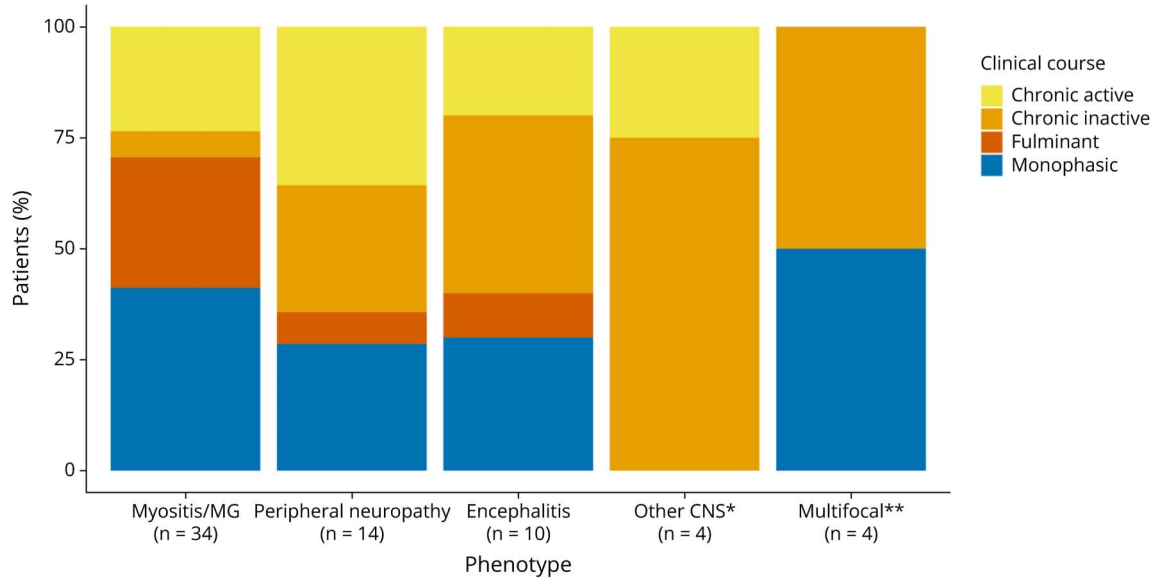


(A and B) Brain MRI fluid-attenuated inversion recovery sequences in a patient with anti-Ma2 encephalitis after receiving pembrolizumab for lung cancer, showing hyperintensity and swollen appearance of the right uncus of the hippocampus (A: axial view, arrow; B: coronal view, arrowheads). (C and D) Skeletal muscle biopsy of a patient with myositis and myasthenia after combination treatment with anti–PD-1 and CTLA-4 inhibitors for lung cancer (C: hematoxylin and eosin–stained section showing diffuse and abundant endomysial inflammatory infiltrate associated with muscle fiber necrosis and regeneration; D: CD8 immunohistochemistry showing $CD8^+$ T-cell inflammatory infiltrate).

neurological irAEs other than myocarditis were significantly more frequent in patients with monophasic irAEs (48%) compared with patients with chronic active or inactive n-irAEs (19% and 7%, respectively, p <0.01).

In the acute phase, patients with chronic n-irAEs (both active and inactive), compared with those with monophasic n-irAEs, received more frequently PLEX and/or IVIGs (44% and 40% vs 13%, p = 0.003). The median duration of steroid treatment

Figure 3 Clinical Course in Different Types of n-irAEs



*Other types of CNS involvement included 3 demyelinating syndromes (1/3 chronic active and 2/3 chronic active) and 1 CNS vasculitis. **Multifocal n-irAEs included myositis and unilateral optic neuritis (chronic inactive), cerebellitis and cranial neuritis (chronic inactive), cerebellitis and cranial neuritis (monophasic), brain demyelinating lesions and inflammatory polyradiculopathy (monophasic).

Table 2 Demographics, Clinical Features, Treatment, and Outcomes of Patients With n-irAEs Grouped According to Their Clinical Course

	Monophasic (N = 23)	Chronic active (N = 16)	Chronic inactive (N = 15)	Fulminant (N = 12)	*p* Value
Age, y	69 (63–74)	68 (62.5–79.5)	62 (54–71)	76.5 (72.5–80)	0.001
Sex					0.323
Male	20 (87)	12 (75)	10 (67)	11 (92)	
Female	3 (13)	4 (25)	5 (33)	1 (8)	
Cancer					0.934
NSCLC	8 (35)	5 (31)	5 (33)	3 (25)	
Melanoma	6 (26)	5 (31)	3 (20)	5 (42)	
Urological	5 (22)	2 (13)	2 (13)	2 (17)	
Other	4 (17)	4 (25)	5 (33)	2 (17)	
ICI class, N (%)					0.641
PD-1	18 (78.2)	11 (68.8)	7 (46.6)	8 (66.7)	
PD-L1	3 (13)	4 (25)	6 (40)	3 (25)	
CTLA-4	1 (4.4)	0 (0)	1 (6.7)	0 (0)	
Combo	1 (4.4)	1 (6.2)	1 (6.7)	1 (8.3)	
Latency, wk	6 (3–22.7)	14.7 (3.8–39.6)	26.3 (8.7–43.1)	5.1 (3–7.5)	0.008
Neurologic involvement, N (%)					0.044
PNS	18 (78)	13 (82)	6 (40)	11 (92)	
CNS	3 (13)	3 (18)	7 (47)	1 (8)	
Multifocal	2 (9)	0 (0)	2 (13)	0 (0)	
Neurologic phenotype, N (%)					0.289
MG and/or myositis	14 (61)	8 (50)	2 (13)	10 (84)	
Neuropathy	4 (17)	5 (31)	4 (27)	1 (8)	
Encephalitis	3 (13)	2 (13)	4 (27)	1 (8)	
CNS demyelinating	0 (0)	1 (6)	2 (13)	0 (0)	
CNS vasculitis	0 (0)	0 (0)	1 (7)	0 (0)	
Multifocal	2 (9)	0 (0)	2 (13)	0 (0)	
Paraneoplastic-like presentation, N (%)	2 (8.7)	2 (12.5)	5 (33.3)	2 (16.7)	0.263
Non-neurologic irAEs, N (%)					<0.001
Myocarditis	3 (13)	2 (12.5)	1 (6.7)	8 (66.7)	
Other	11 (47.8)	3 (18.8)	1 (6.7)	2 (16.7)	
PLEX or IVIG, N (%)	3 (13)	7 (44)	6 (40)	9 (75)	0.003
Second-line treatments, N (%)	0 (0)	3 (19)	1 (7)	1 (8)	0.102
Steroid discontinuation, N (%)	10/19 (53)	7/16 (44)	8/15 (53)	3/10 (30)	0.523
Steroid treatment duration, mo, median (IQR)	2.5 (2–3)	7 (3–12)	2.5 (2–3)	1 (0.5–1.5)	0.042
ICI rechallenge, N (%)	5 (22)	2 (13)	1 (7)	0 (0)	0.422
Follow-up time, mo	12 (5.2–20)	11 (4.8–16.5)	9 (6–18)	1.2 (0.7–1.8)	<0.001
CTCAE 5.0, median (IQR)	3 (2–3)	3 (2–3)	3 (2–3)	5 (5–5)	<0.001

Continued

Table 2 Demographics, Clinical Features, Treatment, and Outcomes of Patients With n-irAEs Grouped According to Their Clinical Course *(continued)*

	Monophasic (N = 23)	Chronic active (N = 16)	Chronic inactive (N = 15)	Fulminant (N = 12)	*p* Value
mRS score, median (IQR)					
At nadir	2 (2–3)	3 (3–3.5)	3 (2–4)	5 (5–5)	<0.001
At last follow-up	1 (0–1)	2 (0.5–3)	1 (1–3)	6 (6–6)	<0.001
Disability at last visit, N (%)[a]					<0.001
Mild (mRS<2)	22 (96)	10 (62)	10 (62)	0 (0)	
Severe (mRS 3–5)	1 (4)	6 (38)	4 (27)	0 (0)	
Death, N	1	8	4	12	<0.001
Related to n-irAE	0 (0)	0 (0)	1 (7)	12 (100)	
Cancer progression	1 (4)	7 (44)	3 (20)	0 (0)	
Other causes	0 (0)	1 (6)	0 (0)	0 (0)	

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; ICI = immune checkpoint inhibitor; n-irAE = neurologic immune-related adverse event; NSCLC = non–small-cell lung cancer; PD-1 = programmed death protein 1; PD-L1 = programmed death protein ligand 1.
Data are presented as number with percentage (%) or median with interquartile range variation (IQR).
[a] In patients who died due to non-neurological causes, the last neurologic evaluation before death was considered.

in patients with nonfulminant n-irAEs was 3 months (IQR 2–4) and was longer in patients with chronic active n-irAEs (7 months, IQR 3–12) compared with those with monophasic and chronic inactive n-irAEs (2.5 months [IQR 2–3], $p = 0.042$).

Patients with chronic active and inactive n-irAEs, compared with those with a monophasic toxicity, had higher rates of severe neurologic disability at the last visit (38% and 27% vs 4%, $p < 0.001$), higher mortality (50% and 27% vs 4%, $p < 0.001$), which was almost always related to cancer progression, as given in Table 2, and shorter survival (log-rank $p < 0.01$; Figure 3). ICI rechallenge was attempted in patients with monophasic n-irAEs (5/23, 22%) and, more rarely, in patients with chronic active n-irAEs (2/16, 12%) and chronic inactive n-irAEs (1/15, 7%), and none developed neurologic relapses (Figure 4).

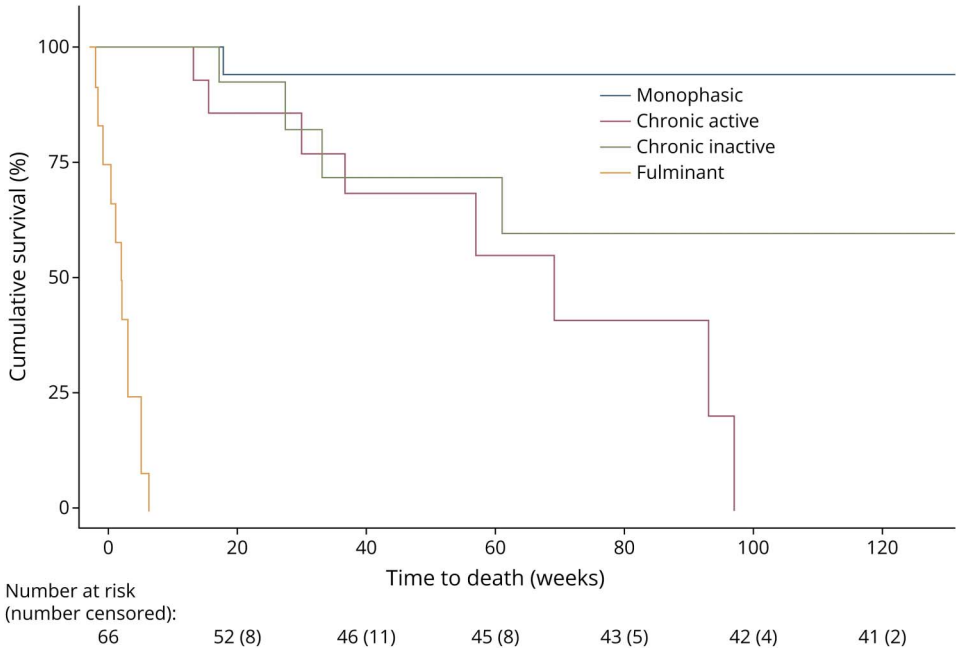
Discussion

This study assessed the clinical course of n-irAEs in a large nationwide multicenter cohort. The prevalence of fulminant and chronic n-irAEs was high (respectively, ~20% and ~50%), highlighting a significant burden of mortality in the acute phase and morbidity in the postacute phase. Patients with chronic n-irAEs had higher overall mortality and shorter survival than those with monophasic n-irAEs, with mortality in the postacute phase predominantly related to cancer progression.

The acute phase of n-irAEs has thus far received the bulk of attention, owing to its dramatic clinical presentation and need for urgent treatment. However, little is known about the clinical course of n-irAEs beyond the acute phase. In our cohort, more than half of the patients with n-irAEs who survived the acute phase developed a chronic condition. Similar rates of chronicity have been reported for irAEs involving other nonvisceral systems, such as endocrinopathies, arthritis, xerostomia, and ocular events.[20,21] Most chronic irAEs are related to an irreversible tissue damage produced by the inflammatory process and are, therefore, likely unresponsive to prolonged immunosuppression (i.e., chronic *inactive*). However, by applying the definitions recently proposed by the SITC,[13] we found that in our cohort, more than half of the chronic n-irAEs could be considered *active*, due to ongoing immunosuppression, relapse on corticosteroid tapering, or neurologic deterioration during immune-active treatments.

From an etiopathogenetic perspective, in chronic active n-irAEs, the immunologic perturbation induced by the immune checkpoint blockade may unleash a preexistent—but clinically silent—autoimmune process, either related to an individual patient's predisposition or dependent on the underlying cancer, through the cross reactivity of the immune system toward neural or muscle autoantigens ectopically expressed by cancer cells, in line with the mechanisms of paraneoplastic autoimmunity.[22,23] In this study, paraneoplastic-like n-irAEs occurred in one-fifth of patients and almost always developed into chronic events, in line with previous findings of poorer treatment response[11,24-26] and more frequent long-term neurologic sequelae[10] in this subset of patients. The high frequency of chronicity in PNS-like n-irAEs may be explained by a predominance of cytotoxic effector mechanisms leading to irreversible neuronal loss (chronic inactive n-irAEs),[27] but also by a persistent smoldering autoimmunity (chronic active n-irAEs),

Figure 4 Kaplan-Meier Curves Showing Cumulative Probability of Survival After n-irAEs, Stratified by Clinical Course



Log-rank test: $p < 0.01$. Compared with patients with monophasic n-irAEs, patients with both chronic active and inactive n-irAEs had shorter survival.

as recently suggested by the detection of long-lived tissue-resident memory T cells in the autoptic lesions of patients with ICI-naïve PNS.[28] In this regard, the mechanisms underlying chronic active and inactive n-irAEs are likely to represent opposite ends along a continuum of inflammatory activity. By contrast, in monophasic n-irAEs, the autoinflammatory process is probably strictly dependent on the immune checkpoint blockade and, therefore, self-limiting at ICI withdrawal. Of interest, we herein found an association of monophasic n-irAEs with concurrent non-neurological irAEs, which is consistent with previous findings[10] and suggests that in a subset of patients, ICIs induce a more generalized but self-limiting activation of the immune system.

Regardless of the underlying pathophysiologic mechanisms, the distinction between monophasic and chronic n-irAEs seems to be clinically relevant because patients with chronic n-irAE had a shorter survival, almost always because of cancer progression. In this regard, the reduced life expectancy in patients with chronic n-irAEs could be explained by the abstention from further cancer treatment (because of a poorer performance status due to severe neurologic disability[29]) or, in patients undergoing prolonged immunosuppression, by a possible deleterious effect on oncological outcomes. Nevertheless, whether prolonged immunosuppression may affect cancer survival and the efficacy of ICI therapy is still controversial[30,31] and needs to be investigated in prospective studies.

Because cancer progression is the first cause of death in patients surviving the acute phase of n-irAEs, a key question faced by physicians is the safety of ICI rechallenge. In this cohort, we did not observe any relapse in 8 patients who underwent rechallenge with the same ICI, including both patients with monophasic and chronic n-irAEs. Other studies[9,32-34] also reported low rates of neurologic relapses after ICI reintroduction (~0–20%), suggesting that ICI rechallenge is a feasible option, although more caution is advocated in patients with previous life-threatening events (such as myositis and myocarditis) or at risk of irreversible severe neurologic disability (such as PNS-like presentations).

Finally, consistent with previous findings,[9,35] in this cohort, one-fifth of patients died in the acute phase because of the neurotoxicity, and the presence of myocarditis, which always overlapped with myositis/MG in a clinical phenotype known to be refractory to first-line treatments, was independently associated with a fulminant course. These results emphasize the need for early identification and treatment in patients presenting with myositis/MG and myocarditis.

Our study has several limitations. First, its retrospective nature could have hampered data collection. Second, the decision whether to search for anti-neuronal antibodies was taken at a single-center level and was not based on a shared study protocol. Nonetheless, only a minority of patients—all with myositis/MG or peripheral neuropathies—were not tested for neural antibodies. Moreover, neural antibody testing was performed in different, local laboratories, using heterogeneous diagnostic methods, possibly determining antibody misclassification in some cases. However, the diagnostic value of positive results was supported by the consistency of the antibody specificity with the associated cancer and phenotype in most cases (not shown). Third, the

moderate sample size limited the statistical power of the analysis between groups. Finally, the categorization of patients into 4 types of clinical courses was based on the definitions proposed by the SITC, which were not specifically tailored for neurologic toxicities. In particular, because a direct measurement of neuroinflammation is often not clinically feasible, the distinction between chronic active and inactive n-irAEs was based, in most cases, on the physician's decision to pursue immune-active treatments, which might have depended on the clinical severity in the acute phase and/or the resemblance with their idiopathic counterpart—usually managed with long-term immunosuppression—as idiopathic inflammatory myopathies, MG, or chronic inflammatory demyelinating neuropathy. Nevertheless, the SITC consensus definitions for the irAE clinical course[13] allow standardization of the distinction between chronic active and inactive toxicities, therefore representing an important framework for future research tailored on n-irAEs, which will need to identify other clinical parameters and/or biomarkers able to objectively distinguish active forms—which would benefit from prolonged immune-active treatments—from inactive forms, for which long-term immunosuppression would be futile and possibly even deleterious for the oncological outcome.

In conclusion, our study found that more than half of the patients with n-irAEs who survived the acute phase developed a chronic condition, and that patients with chronic n-irAEs have a higher risk of death, mainly related to cancer progression.

Future studies are needed to better characterize the clinical characteristics and the pathophysiology of chronic n-irAEs. Moreover, identifying clinical or ancillary biomarkers of persistent inflammatory activity in n-irAEs is paramount to select patients who would benefit from a prolonged immunosuppression. Because patients with chronic n-irAEs had a higher risk of mortality related to cancer progression, prospective studies are warranted to establish the safety of long-term immunosuppression and ICI rechallenge in this population.

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Appendix *(continued)*

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