CLINICAL PATTERNS AND LONG TERM OUTCOMES OF ARTHRITIS TRIGGERED BY IMMUNE CHECKPOINT INHIBITORS. A MULTICENTER STUDY

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BACKGROUND

Immune-related adverse events (irAEs), including inflammatory arthritis (IA), have become a subject of increasing interest within the rheumatology community. Unraveling the prognosis and treatment needs for individuals experiencing ICI-induced arthritis remains a complex task, as outcomes can vary widely among patients

OBJECTIVE

To analyse the clinical presentation, treatment response, and outcomes of IA induced by immune checkpoint inhibitors (ICIs) in patients with cancer.

METHODS

Retrospective observational study conducted from January 2015 to December 2023 at four tertiary university hospitals.

RESULTS

We included 119 patients (63% male) with a mean age at diagnosis of 66 ± 11 years. Table 1 summarises their general characteristics, cancer types, and ICI molecules. The primary underlying cancers were lung (41%), melanoma (18.5%), renal-urothelial (12.6%), hematologic (6%), and other neoplasms (6%). ICIs comprised monotherapy (91%) and combined regimens (9%). In the monotherapy group, most patients received PD-1/PD-L1 inhibitors, with only one case involving a CTLA-4 inhibitor. Thirteen patients (11%) underwent additional oncologic treatments.

Nine patients (7.5%) developed other rheumatic immune-related adverse events (irAEs), including sicca syndrome (9 cases), myositis (1 case), and sarcoidosis (1 case), while 41 (34.4%) experienced one or more non-rheumatic irAEs, usually before or simultaneously with rheumatic syndromes.

Of the 119 patients, 83 (70%) developed peripheral arthritis, and 36 (30%) exhibited a polymyalgia rheumatica (PMR)-like syndrome.

Among patients with peripheral arthritis, the median time from cancer diagnosis to ICI initiation was 6 months (IQR 25th–75th percentile: 1.8–14 months), and from ICI initiation to joint involvement was 127 days (IQR 51–242 days). Patients receiving combined therapy tended to develop symptoms earlier than those on monotherapy. Arthritis manifestations included polyarthritis (53 cases), oligoarthritis (24 cases), and monoarthritis (6 cases). The final diagnoses were undifferentiated arthritis in 53 (44.5%) patients, rheumatoid arthritis (RA)-like in 19 (16%), psoriatic arthritis-like in 8 (7%) and reactive arthritis-like in 3 (2.5%). Immunological markers showed positive ANA in 23.7% (14/59) and positive RF and ACPA in 3.3% (3/59).

Arthritis treatments included the use of NSAIDs in 58% (48/83) of cases, GCs in 96% (80/83), HCQ in 44.5% (37/83), MTX in 12% (10/83), SSZ in 1.2% (1/83) and anti-TNF in 1.2% (1/83).

Regarding The median follow-up time for patients with arthritis was 9 months (IQR 3.4–16). At the last visit, 36% (30/83) achieved sustained drug-free remission (SDFR). ICI therapy was discontinued in 20 cases, while whereas 10 patients continued with their immunotherapy regimen without experiencing a relapse over a median follow-up of 9 months (IQR 6–23.09).

Among the 53 patients (64%) who were still under treatment for arthritis at the last visit, ICI therapy was ongoing in 49% (26/53) and had been discontinued in 51% (27/53). In the group of 27 patients where immunotherapy was discontinued, active arthritis persisted after a median follow-up of 8.20 months (IQR 3-17).

Persistence of IA was more frequent in patients with longer duration of ICI use, those receiving combination ICI therapies, and in patients with multiple other immune-related adverse events.

Among the 36 patients with PMR-like syndrome, the median time from cancer diagnosis to ICI initiation was 2 months (IQR 0.5–5.5 months), and from ICI initiation to PMR onset was 118 days (IQR 59–219 days). Besides GCs, 17% (6/36) were on steroid-sparing agents (MTX, leflunomide, or HCQ). The median follow-up was 12.4 months (IQR 5.2–21). At the last visit, ICIs were discontinued in 33.3% (12/36) of these patients, with 35% (11/36) achieving SDFR, while 69.5% (25/36) remained on treatment.

Table 1. General characteristics, type of cancer and ICI molecules

	N = 119
Gender (Women/Men)	76 (63%) / 44 (37%)
Age, yrs (mean ± SD)	66 ± 11
Median time from ICI initiation and irAEs onset, months (IQR 25th–75th)	
Arhritis	127 days (IQR 51–242 days
PMR like	118 days (IQR 59–219 days).
Type of cancer*	
Gastrointestinal	2 (1.7%)
Liver	2 (1.7%)
Breast	3 (2.5%)
Gynecologic	2 (1.7%)
Head and neck	7 (6%)
Renal-Urothelial	15 (12.6%)
Prostate	2 (1.7%)
Thyroid	2 (1.7%)
Lung	49 (41%)
Mesothelioma	4 (3.4%)
Melanoma	22 (18.5%)
Hematologic	7 (6%)
Sarcoma	1 (0.8%)
Cordoma	1 (0.8%)

Type of Checkpoint inhibitors	
Monotherapy	106 (89%)
CTLA-4 inhibitor:	1 (0.8%)
Ipilimumab:	1
PD-1/PD-L1 inhibitors	105 (88.2%)
Nivolumab	31
Pembrolizumab	49
Atezolizumab	14
Durvalumab	10
Avelumab	1
Combined Therapy	11 (9.2%)
Nivolumab + Ipilimumab	8
Pembrolizumab + Ipilimumab	2
Durvalumab + Tremelimumab	1
Anti T cell immunoglobulin mucin domain 3 (anti-TIM3)	2 (1.7%)
Additional treatments:	13 (11%)
Pemetrexed	1
Anlalogous OX 40	1
AFM13 (anti16-30)	1
Bevacizumab	1
Lenvatinib	1
Brentuximab	2
Galunisertib	1
NKT 214 (Bempegaldesleukin)	1
Olaparib	2
Levantanib	1
Eftilagimod	1
Epacadostat	1

CONCLUSIONS

The most frequent patterns of arthritis triggered by ICIs are undifferentiated arthritis (44.5%), PMR-like syndrome (30%), and RA-like (16%). Forty-five percent of patients required a csDMARD / bDMARD. At the last follow-up, 65% of cases remained with active arthritis, either persistent or presenting intermittent flares. Persistence of IA after the cessation of immunotherapy was observed in 58.7% (27 out of 46) of the cases.

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