Musculoskeletal immune related adverse events in patients treated with checkpoint inhibitors

a multicentric retrospective study

Meric de Bellefon L.[1], Sokolova T.[1],Malaise O.[2],Wittoek R.[3], Aerts N.[4], Piette Y.[5], Neerinckx B.[6], Verhaert M.[7], Aspeslagh S.[7], Durez P.[1]

BACKGROUND

CheckPoint Inhibitors (CPI) have been labelled for use in almost 50% of all tumours, leading to over 5 million cancer patients treated yearly in the US and the EU.

Up to 40% of the CPI-treated patients will develop immune related adverse events (irAEs), of which 1 to 7% are musculoskeletal irAEs (ms-irAEs).

The need for a multidisciplinary approach for diagnosis and management of the irAE is fully recognized and international recommendations have been published accordingly.

METHODS

Patients on CPI treatment developing inflammatory joint disease, were referred by their oncologist to the local rheumatologist. Data on patient's characteristics, tumour diagnosis and type, nature and severity of the irAE, and the occurence of additional irAEs were collected in a retrospective way from 2018 to 2022.

AFFILIATIONS

1. Rheumatology Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium
2. Rheumatology Department, CHU Liège, Liège, Belgium
3. Rheumatology Department, Ghent University, Ghent, Belgium
4. Rheumatology Department, Ziekenhuis Netwerk Antwerpen, Belgium
5. Rheumatology Department, AZ St. Jan, Brugge, Belgium
6. Rheumatology Department, Gasthuisberg, Leuven, Belgium
7. Oncology Department, UZ Brussel, Brussels, Belgium

Together with the Belgian Society of Medical Oncology, the KVBR/SRBR has launched a taskforce to study the ms-irAEs on a national level. We report a multicentric retrospective study of cases of induced inflammatory joint diseases in patients treated with CPI.

RESULTS

A total of 23 patients were included in this study with a median age of 68 years (SD 11) and a sex ratio of 18 males (69.6%) for 7 females (30.4%). The cancer diagnosis were the following: 9 cases of metastatic melanoma, 4 renal cell carcinoma (RCC), 5 lung cancer, 1 uterine cancer, 3 bladder carcinoma and 1 gall bladder carcinoma.

Four different CPI were used in the 23 patients: 20 were on anti-PD1 monotherapy (10 [43,5%] pembrolizumab, 8 [34,8%] nivolumab, 1 [4,3%] atezolimumab, 1 [4,3%] durvalumab) and 3 (13%) were treated with a combination of ipilimumab and nivolumab. 12 patients experienced at least one additional irAE and one patient experienced two.

The median time-to-arthritis was 4 months (SD 5.1). The clinical presentations were mainly polyarthritis (11/23) and oligoarticular (8/23) (fig.1). Four patients were diagnosed with polymyalgia rheumatica. All types of joints were involved from large to small joints. Only one patient had a flare of a known rheumatoid arthritis.

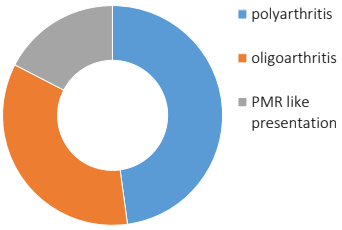

Figure 1. Clinical presentation of CPI induced arthritis

Corticosteroids (CS) were administered to 22 (95.6%) patients and 9 (39%) patients received Disease Modifying AntiRheumatic Drugs (DMARDs) including 3 biologicals. Immunotherapy was discontinued in 12 (52%) patients, in 3/12 cases because of tumour progression and not because of the irAE.

	Lung n=5	Melanoma n=9	Bladder n=3	RCC n=4
Age, mean ± SD (median)	64.40 ± 9.3 (67)	65.89 ± 10.3 (67)	69.00 ± 3.6 (68)	80.00 ± 8.2 (83)
Time to Arthritis, mean ± SD (median)	6.4 ± 3.9 (6)	3.13* ± 3.1 (2.5)	9.33 ± 1.52 (9)	8.62 ± 9.6 (6)
Women/men, %	20%/80%	44.4%/55.6%	100% men	100% men
CheckPoint Inhibitor	60% pembrolizumab	33.3% pembrolizumab 44.4% nivolumab	100% pembrolizumab	50% nivolumab
Clinical presentation	40% polyarthritis	66.7 polyarthritis 22.2% oligoarthritis	All types	50% (n=2) oligoarthritis
Large joint involvement, %	60%	66.7%	66.7%	75%
Small joint involvement, %	60%	55.6%	100%	25%

Table 2. Patient and arthritis characteristics according to cancer type. A significant statistical difference is identified for the time-to-arthritis between melanoma patients and patients with bladder cancer with a shorter time-to-arthritis after the CPI initiation for the melanoma patients.

	N = 23
Age, median (SD)	68 years (11)
Female sex, N (%)	7 (30,4%)
Tumor type (%)	9 melanoma (30,1) 4 RCC (17,4) 5 lungs (21,7) 1 uterus (4,3) 3 bladder (13) 1 gall bladder (4,3)
Additional irAE	0: 11 1: 12 >1: 1 In combo CPI 3/3 had 1 additional irAE
Type of additional irAE	pancreatitis uveitis osteonecrosis hip hypothyroidism thrombopenia sicca sicca, neuronitis, pneumonitis retinal detachment myocarditis diverticulitis non-arteritic anterior ischemic optic neuropathy DD optic neuritis IR-hypercalcemia (sarcoid-like)
ms-irAE type, N (%)	Polyarthritis: 11 Oligoarthritis: 8 Polymyalgia rheumatica: 4*
Joint distribution	Large joints: 15 Medium joints: 15 Small joints: 13
Time-to-arthritis, median (SD) in months	4 (5.1)
Synovial biopsies, N (%)	5 (21)
ACPA positive, N (%)	1 (4)
RF positive, N (%)	3 (13)
ANA positive, N (%)	3 (13)**

Table 1. Patient, cancer and immunerelated adverse events characteristics.
* 1 patient with PMR like presentation also had swollen wrists (oligoarthritis)
** low titers 1/80

	Pembrolizumab (n=10)	Nivolumab (n=8)	IPI-NIVO (n=3)
Age (mean)	69.0	70.88	59.67
Time to Arthritis (months)	6.8	5.9	1.5
Women/men %	10%/90%	50%/50%	33.3 F (n=1)
Clinical presentation	40% polyarthritis 30% oligoarthritis	50% polyarthritis 25% oligoarthritis	67% polyarthritis 33% oligoarthritis
Large joint involvement, %	60%	62.5	100
Small joint involvement, %	70%	37.5	66.7

Table 3. Patients and arthritis characteristics according the CheckPoint Inhibitor used. No significant statistical differences have been found in relation with the treatment used.

CONCLUSION

ms-irAEs are a severe and often chronic problem clearly impacting patients' quality of life. The ms-irAEs in patients treated with CPI mainly have an oligo- and polyarticular presentation, may have a quick onset, bear almost no serological biomarkers and appear in patients with no history of autoimmune diseases. Corticosteroids are the basis of treatment and DMARDs have been added in 39% of cases.

Melanoma patients seem to have a shorter time-to-arthritis compared to patients with bladder cancer. This might indicate a faster onset in these patients, but due to limited sample size, conclusion are difficult to draw. Our data illustrate the crucial need for strong collaboration between oncologists and rheumatologists in these patients.