P505

Immune-related neuromuscular and cardiac adverse events: a retrospective, multicentre analysis and systematic review of case reports and series

Andrea Boutros[1,2], Annarita Bottini[2], Giovanni Rossi[1], Enrica Teresa Tanda[1], Francesco Spagnolo[1], Elena Croce[1,2], Giulia Barletta[1], Paolo Fava[3], Alessandro Parisi[4], Francesco De Rosa[5], Marco Palla[6], Riccardo Marconcini[7], Marina Grandis[8,9], Paolo Spallarossa[10], Matteo Sarocchi[10], Eleonora Arboscello[11], Lucia Del Mastro[2,12], Matteo Lambertini[2,12], Paolo Pronzato[1], Carlo Genova[2,12]

[1]Oncologia Medica 2, IRCCS Ospedale Policlinico San Martino, Genova, Italy; [2]Department of Internal Medicine and Medical Specialties, School of Medicine, University of Genoa, Genoa, Italy; [3]Department of Medical Sciences, Dermatologic Clinic, University of Turin, Torino, Italy; [4]Department of Life, Health & Environmental Sciences, University of L'Aquila, L'Aquila, Italy; [5]IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori", Meldola (FC); [6]Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori - IRCCS - Fondazione "G. Pascale", Naples, Italy; [7]Azienda Ospedaliera Universitaria Pisana, Medical Oncology Unit, Pisa, Italy; [8]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and Maternal and Infantile Sciences (DINOGMI), University of Genova, 16126 Genova, Italy; [9]IRCCS Ospedale Policlinico San Martino, 16132 Genoa, Italy; [10]Cardiovascular Disease Unit, Ospedale Policlinico San Martino IRCCS, Genoa, Italy; [11]Emergency Department, IRCCS Ospedale Policlinico San Martino Genoa, Genoa, Italy; [12]U.O.C. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy.

UNIVERSITÀ DEGLI STUDI DI GENOVA

OSPEDALE POLICLINICO SAN MARTINO

BACKGROUND

- Immune-checkpoint inhibitors (ICIs) have revolutionized clinical practice in oncology, with significant benefits in terms of efficacy, quality of life and safety in several tumor types[1].
- In most cases, the immune-related adverse events (irAEs) are clinically easy to manage and paucisymptomatic. However, in rare cases irAEs may be life-threatening, especially those affecting the neuromuscular and cardiac system[2].
- The management of these irAEs is not clear due to the lack of consistent data. Therefore, we collected cases from selected Italian centers and carried out a systematic literature search to collect case reports and case series on this topic to improve our understanding of these irAEs.

METHODS

- We collected retrospective data from patients treated in 6 Italian centers with ICIs (PD-1 or PD-L1 and/or CTLA-4 inhibitor) for any solid tumor who experienced neuromuscular and/or cardiovascular toxicity.
- Then, to increase the caseload, we performed a search of case reports and series of neuromuscular/cardiac irAEs from ICIs with any solid tumor.

References: [1] Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018; 359(6382):1350–1355. [2]Haanen JB, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv119–42.

Abbreviations CK: creatinkinase; ECG: electrocardiogram; ICI: immune checkpoint inhibitor; irAE: immune-related adverse event; LVEF: left ventricular ejection fraction; NSCLC: non-small cell lung cancer.

RESULTS

The muscular/cardiac irAEs outcome analysis has been conducted including both cases from our institutions (n=18) and the case reports identified in our systematic literature search (n=112), for a total of 130 patients.

- Among these patients, 44 had complete resolution of their neuromuscular/cardiac irAEs, in 21 there was a clinical improvement with mild sequelae, and 52 patients died as a result of the irAEs.
- Factors statistically significantly associated with worse outcomes were the earlier irAE onset, within the first 2 cycles of ICI (Fisher P< 0.0001), clinical manifestation of both myositis and myocarditis if compared to patients who developed only myositis or myocarditis (Chi-square P= 0.0051), and the development of arrythmia (Fisher P= 0.0051).

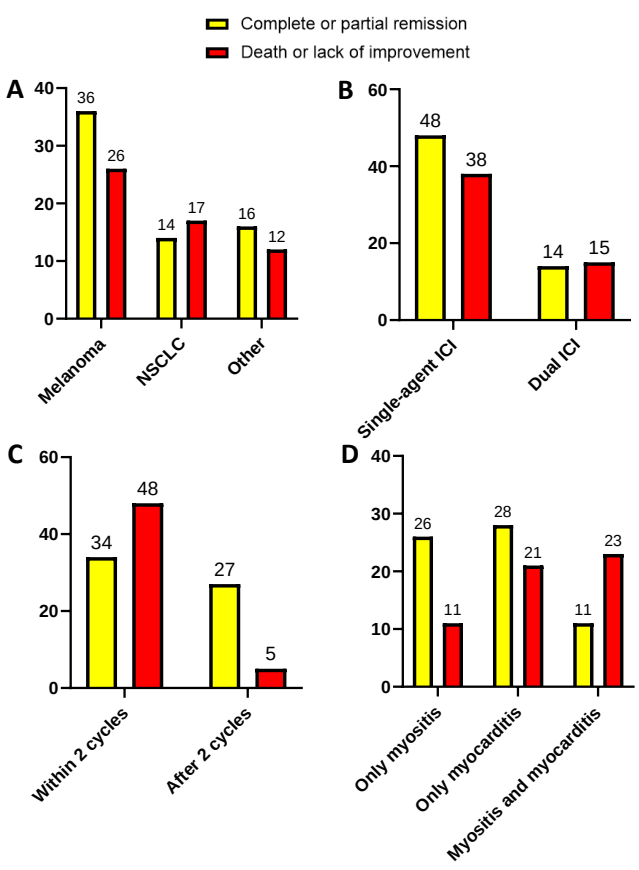

Figure 1. Outcomes of cardiac/muscular irAEs based on: A) primary tumor (Chi-square P= 0.4755), B) use of single-agent ICI (anti PD-1 or PD-L1) or dual ICIs (anti PD-1/PD-L1 plus anti-CTLA4) (Fisher P= 0.5233), C) time of onset of the muscular/cardiac irAE (Fisher P< 0.0001), and D) clinical manifestations of the muscular/cardiac irAE (Chi-Square P= 0.0051).

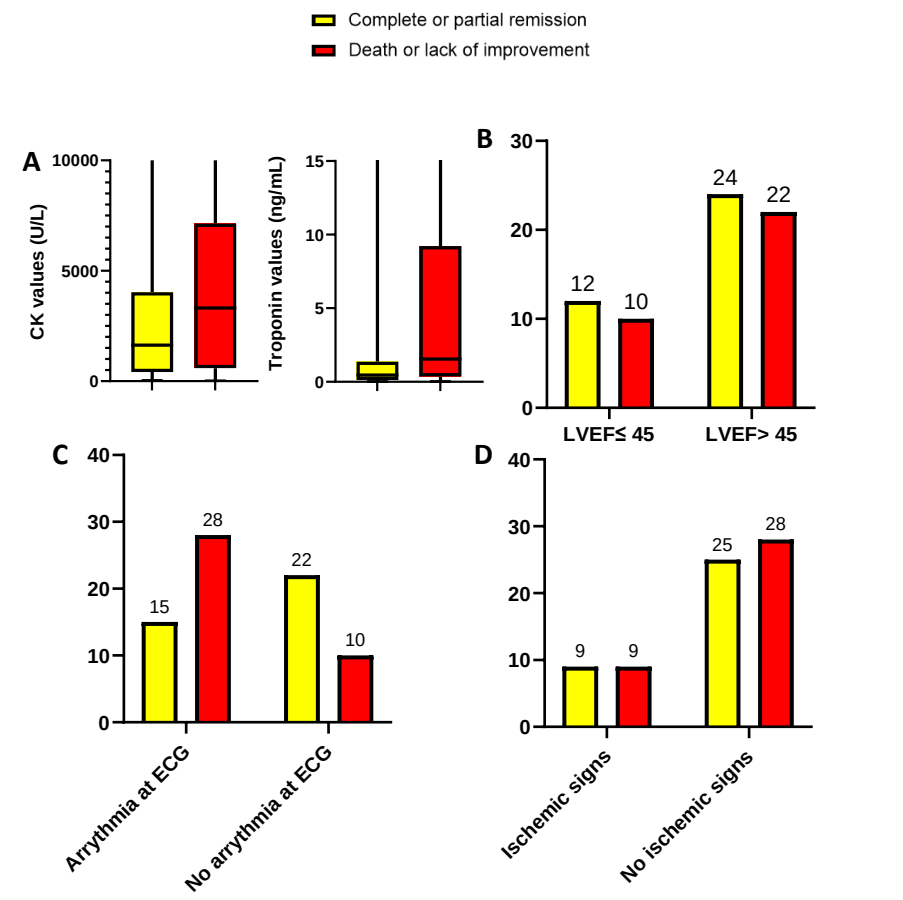

Figure 2. Outcomes of cardiac/muscular irAEs based on: A) CK values (Mann-Whitney P= 0.2467) and troponin values (Mann-Whitney P= 0.0346), B) left ventricular ejection fraction (LVEF) (Chi-Square P= 0.9999), C) finding of arrythmia at ECG (Chi-Square P= 0.0051), and D) ischemic signs at ECG (Chi-Square P= 0.9999).

CONCLUSIONS

To our knowledge, this is the widest collection of individual cases of immune-related myocarditis/myositis. Early irAE onset, concurrent development of both myositis and myocarditis and occurrence of arrythmias are associated with worse outcomes and should encourage an aggressive immunomodulatory treatment.

E-mail: boutros.andrea@gmail.com
@boutrosand

Acknowledgements, *Study sponsored by*: Ministero della Salute

intergruppo melanoma italiano imi