Workshop on psycho-oncology: New therapeutic challenges in Oncology – immunomodulators and the need for a multidisciplinary approach

- J. Espírito Santo: Cancer Immunotherapy: The present and the future
- G. Da Ponte: What psychiatrists need to know about immunotherapy side effects?
- S. Ouakinin: Depression in cancer – Is neuroinflammation the real link?
- J. Póvoa: Cognitive impairment related to cancer: Potential neuroinflammatory contribution

Theme
In this symposium, it will be described the new treatments modalities in cancer in terms of immunotherapy. The goal is to promote the multidisciplinary approach between psychiatry and oncology to allow better care to cancer patients, enabling a rapid diagnostic and treatment of side effects. Jorge Espírito Santo, as Oncologist, will talk about immunomodulators and it’s indications in cancer; Guida da Ponte as psychiatrist will develop the main psychiatric side effects of this new therapeutic modality; Silvia Ouakinin, as psychiatrist, will talk about the role of inflammation in the Central Nervous System and it’s consequences and Susana Almeida, as psychiatrist, will develop an updated vision about chemo-brain in consequence of an immune system disruption.

Takeaways
The main goals of this symposium are:
- update about the advances in immunotherapy in cancer in cancer;
- describe it’s mechanism of action and clinic indications;
- describe the main side effects in terms of neuropsychiatric manifestations;
- co-relate the mechanism of action with Central Nervous System inflammation;
- describe the new vision of chemo-brain in terms of immune system dysfunction.

This Symposium is submitted by the Psycho-Oncology Section of the Portuguese Society of Psychiatry and Mental Health.

Chair: Silvia Ouakinin, Professor, MD, PhD, Medical School of Lisbon, University of Lisbon, PT

Co-chair: Jorge Espírito Santo, Senior Consultant, MD, Oncology Unit, Centro Hospitalar Barreiro-Montijo, PT
Cancer Immunotherapy - the present and the future

Aim
To review the current status of cancer immunotherapy, to highlight the benefits and risks of its utilization in cancer patients and to predict future directions.

Methods
It will be performed a review of the available literature about cancer immunotherapy, its indications, clinical use, safety profile and results.

Results
In this review it will be highlighted the biological basis of cancer immunotherapy, the current indications for its use, the toxicities expected, the results obtained, individualized by tumor type, and the patterns of survival observed with this therapy. It will also be discussed the future perspectives for cancer immunotherapy.

Conclusion
Cancer immunotherapy is an essential part of cancer treatment for some types of tumors and provides a clinically significant survival advantage for the patients, but there are some pitfalls in the use of these drugs that must be taken into account.

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What psychiatrists need to know about immunotherapy side effects?

Aim
Immunotherapy use the Immune System (IS) to treat cancer and, currently, there are four types of drugs (Immune Checkpoint Inhibitors [ICIs], Adoptive Cell Transfer [ACT], vaccines e cytokines) that uses different mechanisms of action. ICIs causes a permanent activation of the IS by blocking the stimulation of the inhibitory pathways, namely the cytotoxic T lymphocyte antigen-4 and programmed cell death-1 protein (PD-1) receptors, and the interaction PD-1 ligand/PD-1. The main technology used by ACT is CAR (chimeric antigen receptors)-T. Vaccines boost the IS against a neoantigen, and cytokines (interferon [IFN-α-2b] and interleukins [IL-2]) potentiate the IS response.
The aim of this work is to describe the main neuropsychiatric side effects of immunotherapy.

Methods
A Pubmed research, between 2018 and 2013, using the key-words: immunomodulators, toxicities, neuropsychiatric.

Results
The core side effects are due to IS activation. An example of the neuropsychiatric immune-related side effects (irSEs) caused by ICIs is encephalitis anti-receptors N-methyl-D-aspartate, with psychiatric manifestations. CAR-T provokes two major toxicities: cytokine release syndrome, a constellation of inflammatory manifestations, and a neurotoxicity. Although relatively infrequent, side effects of IFN-α-2b and IL-2 are dangerous and it can include confusional states, psychosis and depression. irSEs also can manifest as a constellation of symptoms - sickness behavior – which can mimic a depression.

Conclusion
The main side effects of immunotherapy are immune-mediated. Much more is to be discover and it’s emergent a multidisciplinary approach between oncology and psychiatry to better diagnose and treat patients.

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Depression in cancer – Is neuroinflammation the real link?

Aim
The identification of biobehavioural pathways underlying depression in cancer, and the translation of biomarker findings into new clinical insights, are essential to improve diagnose, treatment and prevention of depression in cancer patients. The aim of this paper is to presented an updated review of current investigation in this topic.

Methods
Methods included a search and non-systematic review of the most relevant articles published in PubMed and PsycInfo databases. For that search, words included “depression” “cancer” and neuroinflammation” and the time interval was from 2008 to 2018. Only English written studies were considered; some classic texts and reference authors were included.

Results
Literature is consensual on the role of inflammatory mediators, such as proinflammatory cytokines in depression; some authors tried to associate somatic and psychological symptoms of depression with a neuroinflammatory profile in cancer patients. However, the mechanism that were identified seems to lack specificity and a clarification of the pathways through which inflammation, neurotransmitters and neurocircuits may interact and influence the risk for depression needs a better understanding. In what concerns depression in these patients, chronic stress can act upon a vulnerable individual, amplifying the negative impact of several life events, affective losses and conflictual situations.

Conclusion
The links between depression and inflammation are evident, nevertheless some investigations performed in the last decade produced mixed results. Research, in general, points to the association between biological, psychosocial and behavioural factors in cancer, as well as in its affective consequences and depressive morbidity.

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Cognitive impairment related to cancer: a potential neuroinflammatory contribution

Aim
Cognitive impairment related to cancer (CRIC), previously known as chemobrain, has multiple consequences to patients, impairing quality of life, functional autonomy and treatment decision-making processes. Despite a wealth of growing evidence to sustain its multifactorial pathogenesis, still remains as a controversial entity. Risk factors have been hypothesized. Cancer itself and its biologic mechanisms such as inflammatory processes, surgery and general anesthesia, chemotherapy, radiotherapy and endocrine therapy might exert an influence on cognition. Possible host vulnerability factors further might impact the brain such as oxidative stress, genetic polymorphisms, menopausal status, lower cognitive reserve and psychosocial factors such as cancer related fatigue and distress.

Methods
A systematic review and meta-analysis was performed using the search terms: chemobrain; CRIC; cancer; etiology; neuroinflammation; stress; cortisol; genes; polymorphisms; cytokines; interleukines.

Results
A strong association has been found linking chronic stress and cognitive impairment in cancer patients. Important potential bias are treatment-associated factors; cognitive reserve and depressive and anxiety states. Despite the putative etiologies, one common biologic finding is the evidence of altered brain structure and function. Human neuroimaging studies are supporting the neurobiological basis for these neurocognitive changes both in brain morphology and in activation patterns.

Conclusion
The most recent evidence supporting the neuroinflammatory contribution to the CRIC and other exploratory hypothesis require further investigation before we can assume causation. Prospective studies could prove more adequate to sustain the data so far available.

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