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"Chemobrain": the aging brain and oxidative stress

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Commentary to article:
Gaman AM, Uzoni A, Wagner AP, Andrei A, Pectu EB. *The role of oxidative stress in etiopathogenesis of Chemotherapy Induced Impairment (CICI)-''Chemobrain"*. Aging Disease 2016;3:302-12.

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"Chemobrain" or chemotherapy induced cognitive impairment (CICI) represents a new clinical entity, characterized by executive dysfunction, deficit of memory and learning and motor function impairment after a chemotherapy (CT) regimen [1 2]. Cancer is an age-related disease and, due to the aging population, is going to result a relevant disease of the elders. With the advent of new surgical and chemotherapy options, oncogeriatric patients will turn to be long-term survivors and chemobrain will represent an issue of growing geriatric interest.

To a greater extent, CICI may be regarded as a drug side effect that may be a short-term event or lasting up to 10 years after chemotherapy cessation [3 4], with gradual cognitive decline and great variability among patients.

Several studies have focused on the effect of cyclophosphamide and doxorubicin in breast cancer patients [5 6]. A recent metanalysis [7] has revealed that cancer patients treated with CT may develop verbal memory and executive function impairment that interfere with daily living and quality of life. Moreover, the cognitive deficit may last over 20 years, addressing the need for a better clinical identification of this issue [8].

The impaired neuropsychological findings correlate with neuro-structural changes. Indeed, neuro-structural brain radiology and functional imaging have recently demonstrated an association between chemobrain and lower activation of dorso-lateral, caudal frontex cortex, and reduced glucose metabolism in frontal lobes after CT [9 10].

A series of different chemotherapy compounds have been implicated in the pathogenesis of chemobrain, including platinum compounds, proteasome inhibitors, tyrosine kinase inhibitors and interferon alpha.

The main mechanisms of chemotherapy induced cognitive changes include direct neurotoxicity, genetic predisposition, immune dysregulation, shortened telomeres, inflammation and oxidative stress.

Recently, an interesting review of Gaman et al. [11], pointed out the state of the art and the new horizons of chemobrain with respect to the aging process, the brain aging and the underlying oxidative stress.

Both chemobrain and brain aging seem to be associated with reactive oxygen species (ROS) production and accelerated oxidative stress. CICI may be directly due to the ROS burst generated during chemotherapy. The most studied in vitro and in vivo murine models include doxorubicin (anthracycline) [12 13]. This common CT agent is considered to increase superoxide free radicals' production with oxidation of ApoA1 and the promotion of TNF alpha synthesis. This last cytokine mediator interacts with its receptor on the blood brain barrier (BBB) surface and reaches the brain parenchyma, generating neuronal apoptosis and death, mitochondria mutation (with increased p53) and increased lipid peroxidation, ultimately responsible for chemobrain occurrence (Fig 1).

In particular, brain lipid peroxidation (leads to toxic

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compounds such as aldehyde (4-hydroxinonenal) with increased neuronal death. In parallel, reduced glutathione levels and increased glutathione-S – transferase were also detected in brain after CT.

Further understanding of the mechanisms of different CT compounds is accumulating as well. Carmustine is associated with a significant increase of oxidative stress (malondialdehyde) and overexpression of caspase [3], activation of c-jun N- terminal kinase (JNK) and ERK pathways [14]. Interestingly, carmustine mediates the production of metallothionein in rat models that has an anti-oxidant protective effect.

Methotrexate is associated with increased levels of TNF alpha, increased lipoperoxidation, increased HP70 protein and reduced glutathione levels [15]. Interestingly, methotrexate was found to decrease in vitro stem cells in hippocampus, that could count for the onset of cognitive impairment.

Cyclophosphamide is associated with increased levels of lipid peroxidation, TNF alpha and interleukin-6, increased production of COX2, I NOS, p38 -MAPK and NfkB 16.

However, how CT oxidative stress mediated brain changes may be linked to brain aging has not yet been answered.

Thus, CT compounds seem to mediate ROS release by increasing plasma cytokines, capable of penetrating the BBB.

Normal brain aging is characterized by widespread but not homogeneous neuronal death, especially in frontal lobes and hippocampus, with reduction of grey and white matter. White matter is more vulnerable to oxidative stress and then, both chemobrain and brain aging could start from the same brain regions. During brain aging, neuronal remodelling and integrity result from the coping with perturbation of different metabolic and molecular signalling, causing endothelial damage and neuronal and cellular death [17].

Oxidative stress and vascular injury are also the biological background for cerebral atherosclerosis and small vessel disease that may be involved in both vascular and Alzheimer's type dementia.

To a greater extent, the aging process is itself a potent epigenetic modulator of brain, by increasing ROS generation and mitochondrial dysfunction with proteins and lipid and inflammatory damage, altered cell signalling pathways, apoptosis and altered gene expression [18]. Indeed, the Harman's hypothesis of free radicals claims for the accumulation of oxidative damage to lipids,

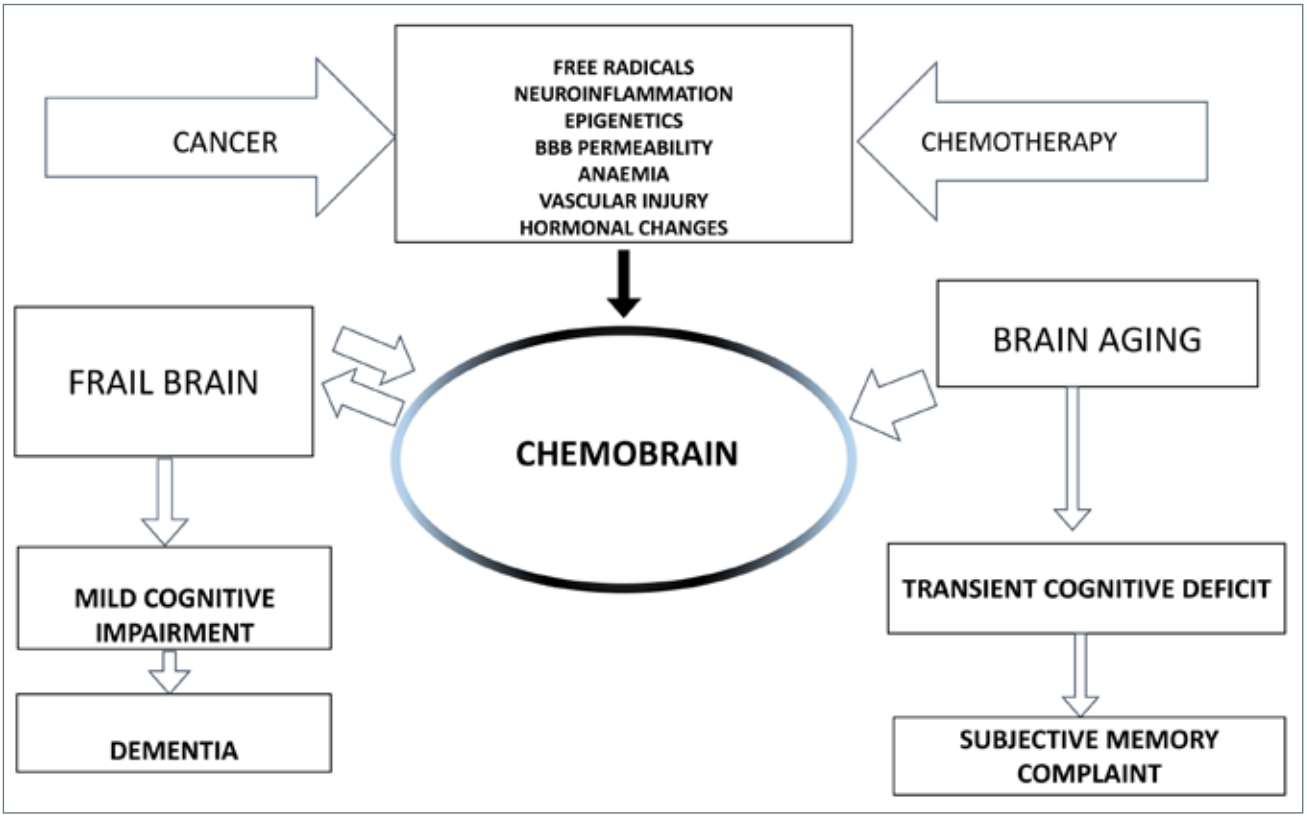

Figure 1. The multifactorial origin of chemobrain and potential neurodegenerative trajectories on the basis of the aging brain.

protein, DNA. Complementary to it, there is the mitochondrial theory of aging that mainly affect insulin/IGF-1 signalling, target for rapamycin (mTOR).
Interestingly, increasing in vivo evidence underlined that aging may promote brain alterations of TNF alpha in a similar way to chemotherapeutic compounds.
The interplay between the aging brain, chemobrain and dementia represents a challenge for geriatricians and bio gerontologists in the near future.
Research should consider cancer and chemotherapy, as potential vulnerability factors, when assessing cognitive functioning and its trajectories in eldelry patients.
Chemobrain and CT should be framed in a larger conceptual framework; CT associated mechanisms mediating reversible or permanent dysregulation of an aging brain could be disentangled and integrated in the different trajectories of cognitive performance in elders.
In addition, the psychological stress after the diagnosis of cancer, the psychosocial resources and the comorbidity burden may represent further moderator of the cognitive performance.
Considering it as a starting point, more explanatory models are needed to support preclinical evidence and to develop effective clinical evidence.
Chemobrain is expected to rely on different pathogenetic mechanisms; chemotherapy regimens are responsible for direct neurotoxic insult mediated by oxidative stress and neuroinflammation. All these mechanisms are responsible for increased neuronal dysfunction and death. There is great heterogeneity among different chemotropic compounds according to their blood brain barrier permeability and penetration; these different physio pathological pathways may count for different brain burden and impact on cognitive performance.
The aging brain may be temporary perturbed by a CT insult, showing cognitive decline after one- three months of therapy. However these deficits had generally resolved at one year follow up or persisting as subjective memory or cognitive impairment.
By contrast, a frail brain, that may be defined as a reduced functional reserve organ with poor homeostenotic adaptation, could be heavily perturbed by a CT stressor. In turn, CT may initiate a neurodegenerative trajectory with a mild cognitive impairment that may ultimately end into a dementia conversion.
Not least, the inverse relationship between cancer and dementia of Alzheimer's type represents a further area of inquiry that deserves clinical evidence, especially in the older populations.

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Conflict of interest

The authors declare that they have no conflict of interest.

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