

Review Of The Forensic Medicine Perspective On Chemotherapy-Induced Cognitive Impairment

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ABSTRACT

Chemotherapy treatments in some neoplastic patients can result in unfavourable side-effects that can be accompanied by physical deterioration from changes in executive functioning, processing speed, and reaction times with a resulting inability to perform daily living activities (ADL) or a working disability from the loss of working memory and the inability to organise basic skills, affecting the quality of daily life. The literature has identified chemotherapy-induced cognitive impairment (CICI), also known as post-chemotherapy cognitive impairment (PCCI), chemo-brain, or chemo-fog, since the late 1980s; nevertheless, the neurobiological causes of this illness are still not fully understood.

According to the findings of the majority of studies done on patients with various neoplastic diseases, there is strong enough proof that certain drugs like doxorubicin, cyclophosphamide, cytarabine, methotrexate, 5-fluorouracil, and cisplatin play a significant part in the neurological impairment linked to chemo-fog.

Therefore, it appears that the patients' physical incapacity is linked to the cytotoxic effects that chemotherapy medications have on the central nervous system, which may result in a temporary or permanent neurological impairment.

Cognitive dysfunctions may affect a person's ability to make decisions for themselves by causing a temporary or recurring mental condition that may affect the preservation of their voluntary faculties and have an impact on the legal validity of any documents they sign. The fact that this pathological disease has non-negligible medico-legal ramifications since it affects areas of private law is what is driving the forensic medical community's rising interest in it.

INTRODUCTION

The toxic and side effects of anticancer medication administration are well recognised, but thankfully, the most of them are transient and manageable by the preventive or therapeutic administration of other medications as well as by modifying the patients' lifestyle.

However, several anticancer medications have intricate toxicity profiles that need to be examined since they might seriously harm a patient's physical and mental health, sometimes even permanently. Anthracycline cardiotoxicity, bleomycin-induced lung fibrosis, and cisplatin nephrotoxicity are typical instances.

Chemo-induced cognitive impairment (CICI) or post-chemotherapy cognitive impairment (PCCI), also known as chemo-fog and chemo-brain, refers to a series of changes in cognitive functioning brought on by the administration of chemotherapy medications. This clinical disease is rather uncommon. While chemo-fog symptoms are typically transient, about 35% of clinically cured oncological patients say that they can last for months or even years. [1,2] Since patients typically have illnesses that seem to be mild, such as weariness, confusion, forgetfulness, a short attention span, and a difficulty to concentrate, the clinical picture is frequently modest.

Due to the increased long-term survival rates of lymphoma and breast cancer, these individuals were the subjects of the majority of studies. Although almost no cognitive function appears to be immune to the illness, memory, data processing speed, and executive skills are the most severely impacted. The patients designated as long-term survivors were found to be particularly affected by the most severe damage to these functions, which had a substantial impact on their quality of life.[4] The data from neuropsychological and instrumental research, where there is less support for objectively detectable cognitive impairment, appear to be at odds with this finding.[5]

It should be emphasized that the lack of set parameters that would control the selection of the appropriate neuropsychiatric and statistical tests to be performed represents another barrier to the objectification of the neurobiological bases of the condition.[8] This issue opens a new area of study in forensic psychology, which is typically restricted to the examination of cognitive processes that are left over from the investigation of fundamental psychic illnesses or those that have organic origins (such as dementia). Comorbidities are more frequently seen for the presence of malignancies and difficulties of purely psychiatric competency as the average population ages. Therefore, having a thorough awareness of the potential effects of antineoplastic chemotherapy treatments seems vital.

In the medico-legal context, assessing cognitive abilities typically involves confirming three situations, such as the presence or absence of a known psychopathological condition, the discovery of a primitive brain tumour capable of directly damaging specific functional areas, and the existence or nonexistence of a dementia framework with an organic basis. This strategy is now inextricably linked to the understanding of the cognitive side effects that antineoplastic treatment can have, both long-term and short-term.

Risk factors

It is important to comprehend the risk factors and causes of cognitive impairment brought on by cancer. Regarding the risk factors, there is strong scientific data showing that ageing, a decline in cognitive capacity, and hormonal changes all significantly contribute to PCCI development. Studies on men and women with prostate cancer and patients with breast cancer

have shown that older patients undergoing anticancer therapy who have decreased cognitive reserves do poorly on psychometric tests. These findings suggest a significantly reduced mental processing speed compared to control groups composed of healthy people or cancer patients who did not get chemotherapy.[9]

Physiopathology and pathogenesis of the disorder

The pathogenic mechanisms causing the damage appear to be mostly caused by an increase in peripheral cytokine levels and chemokine balance because the majority of oral anticancer medications are unable to cross the blood brain barrier.[12–14] A change in neural plasticity would result from peripheral cytokines stimulating the central generation and release of more cytokines by neurons and supporting cells.

Although three mechanisms have been proposed, the exact mechanisms by which these cause changes to the central nervous system remain largely unknown. These include excitotoxicity caused by glutamate, the production of free radicals of oxygen (ROS) and nitrogen (RNS), and the subsequent stimulation of the NO-synthase pathway, which shortens telomeres. Studies have revealed that epigenetic changes brought on by anticancer medications have a vital impact in the improvement of memory and learning abilities.[16-17]

Chemofog and specific malignancies

Studies conducted on patients with breast cancer, haematological malignancies, brain cancer, colon cancer, ovarian cancer, and paediatric cancers have provided the majority of the current knowledge on the clinical and neurobiological characteristics of chemotherapy-induced cognitive impairment.

According to studies, some cancers, like colon cancer³², already cause cognitive impairment, which gets worse as the disease progresses and is treated with anticancer medications. Particularly impacted were working memory, verbal learning, and the rate at which information was processed. Significant observations have also come to light on the effects of hormone therapy based on selective oestrogen receptor modulators (like tamoxifen), which cause treated patients (women with breast cancer) to experience cognitive decline comparable to that brought on by anti-cancer therapy. Furthermore, convincing evidence links hematopoietic stem cell transplantation to the emergence of PCCI, pointing to a diminished basic cognitive reserve, a poor sociocultural starting point, and exhaustion.

Neuropsychological tests for PCCI evaluation

There are many different tests that can be used to assess neuropsychic performance, but The International Cognition and Cancer Task Force, established in 2006 with the goal of creating recommendations and guidelines to harmonise and standardise the neuropsychological test battery and the criteria to be used for assessing cognitive impairment of patients suffering from post-chemotherapy cognitive impairment, recommends using the following three tests: the Hopkins Verbal Learning Test, the Stanford-Binet Test of Memory, and the Mini Mental State Examination (COWA).

Forensic implications

The regulatory element of the diseased condition of chemo-brain, such as mental impairment and physical handicap, has not yet been sufficiently framed. To ensure the proper application of private law laws, however, it is important to carefully evaluate the substantial legal implications that the deterioration of cognitive capacities may have. But what significance do physical and mental disabilities have in the area of private law?

The distinction between an impairment, a disability, and a handicap was stressed by the World Health Organization (WHO) in the 1980 publication International Classification of Impairments, Disabilities, and Handicaps (ICIDH).⁴⁶ The WHO then replaced the previous distinction in 2001 with the International Classification of Functioning, Disability and Health (ICF), which introduced the concept of a person's health in the family, social, and working environments, or in daily life, which can lead to disability, or a health condition in an unfavourable environment. [17]

Mental illness was defined as 'mental illness, arrested or incomplete development of mind, psychopathic disorder and any other disorder or disability of mind' in Section 1 of the Mental Health Act of 1983, a law governing people with mental disorders in the United Kingdom. This definition was purposefully broad in a teleological framework with the intention to protect rather than repress. The Enduring Powers of Attorney Act of 1985, the Court of Protection Rules of 1986, and the Disability Discrimination Act of 1995, as amended by the Equality Act of 2010, are among the subsequent UK legislative acts worth mentioning. According to this definition, a person with a disability is "someone who has a physical or mental impairment, and the impairment has a substantial and long-term adverse effect on ability to carry out normal day-to-day activities.'

Additionally, this Act establishes that a disability may result from a variety of impairments. In Europe in 2009, the European Union Agency for Fundamental Rights (FRA) suggested that the EU Member States participate in the first research project concentrating on the 'Fundamental rights of persons with intellectual disabilities and persons with mental health difficulties.' The project's major objective was to examine how disabilities are classified in international and European law and to highlight the legislative initiatives taken by EU Member States to protect people with mental health issues from discrimination by providing them with reasonable accommodations at work.

In Italy, institutions and outside parties' involvement both contribute to the legal protection of those who are incapable. The curator, in particular, incorporates the disabled person's will while not taking his place in the management of patrimonial interests through the institution of curatorship (curatela). Additionally, the discipline relating to the Institutions for the protection of people who are unable to act and protect their interests has been modified by Law January 9, 2004, No. 6 - Support Administration. Through the institutional position of the support administrator, this law commits to managing the needs of vulnerable individuals in a way that is more flexible and less constrictive than statutory measures like interdiction and incapacitation.

Chemo-brain appears to be a pathological condition that can determine a significant compromise of voluntary and decision-making faculties with legal repercussions in private contexts given the scientific evidence supporting the relevant changes in the mental state related to chemotherapy-induced cognitive impairment involving several domains (especially memory, data processing speed, and executive functions).

Particularly intriguing are the ramifications for the practise of private law, specifically the possibility that the cognitive impairment brought on by chemotherapy makes it difficult for the affected person to comprehend the full scope of his decisions, particularly those involving money and requiring understanding of legal documents with intricate and technical clauses.

It is interesting to note that the Ordinary Court of Milan (n. 13,603, November 25, 2010) issued a judgement that highlights the requirement that anyone wishing to contest the validity of a legal act (in this case, a will) must provide rigorous proof of the testator's inability to understand the legal implications of the signature at the time of affixing to legal documents because it is insufficient to show that a degenerative disease that occurred later existed.[15] This principle leads to the conclusion that when a legal act is signed, it must have a legal focus.

But as the Italian Supreme Court of Cassation's 2nd Civil Section recently held (n.27,061, October 10, 2018), the medical examiner must conduct a detailed investigation based on the subject's mental status.

CONCLUSION

Although the studies on chemotherapy-induced cognitive impairment are not always in complete agreement, they do seem to support the idea that the mental alteration caused by chemotherapeutic drugs is permanent (or at least long-term). This suggests that the condition in question is compatible with the existence of an abnormal mental status that can have significant legal repercussions, both in the criminal and private contexts. This is relevant when signing contracts since the intricacy of the clauses may call for a 'sufficient level' of comprehension.

It would also apply to provisions in wills and gifts made to outside parties. In this opinion, it appears crucial for these experts to have a thorough understanding of the potential cognitive disability linked to pharmacological treatments with chemotherapy, both in their potential contribution to existing cognitive deficits due to other causes and in the temporal window of their activity.[23] This is because, generally speaking, these technical, forensic psychiatric assessments are assigned to specialists in psychiatry.

As many scientific studies have shown, PCCI can affect the memory, the speed with which information is processed, and the executive functions in a particularly selective manner; whereas, by mental competency, we mean the general ability to know and understand the reasons for one's conduct and to be aware of the value of one's actions or omissions; volition is the ability of the individual to choose selectively between two or more equally feasible actions; The conclusion of this review is that PCCI may result in substantial legal consequences.

As a result, during medical-legal tests designed to gauge a person's capacity for self-determination and comprehension of legal Cancer patients having chemotherapy must be aware of the potential for antineoplastic chemotherapy to really affect their ability to exercise their legal rights.

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