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Cognitive impairment in cancer patients and survivors—clinical presentation, pathophysiology, diagnosis and management

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Summary Cognitive impairment by neurotoxic substances, administered alone or in a multidrug regimen, affects a large number of patients treated for noncentral nervous system cancer during and after chemotherapy with variable onset, severity and duration, but sustainably affecting the patients' individual health-related quality of life. Depending on the mechanism of action, the ability to cross the blood–brain barrier into the central nervous system and the cumulative total dose of the cytotoxic drugs results in functional and structural brain changes. This neurotoxicity leads to negative effects on neural precursor cells (neurogenesis), microglia (neuroinflammation), neurons (cortical dysfunction with altered brain networks), and astro-/oligodendroglia (white matter tract demyelination) and therefore on patients' cognitive performance. Memory and executive functions, attention/concentration, and processing speed are the cognitive domains commonly impaired by chemotherapy. Importantly, numerous simultaneously occurring risk factors may also have distinct restrictions on cognitive function. For this reason, the term cancer-related cognitive impairment (CRCI), implicating neurotoxicity in cancer patients with simultaneous consideration of other causes on cognitive performance, should be used. The aim of this review is to provide an update of the most recent clinical and pathophysiological findings, self-reported and neuropsychological testing methods, and the current management strategies of CRCI.

Keywords Quality of life · Neurotoxic cancer treatment · Psychosocial factors · Cognitive reserve · Cancer treatment-associated factors

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Introduction

A large number of patients with noncentral nervous system cancer report cognitive deficits during and after chemotherapy, also called cancer-related cognitive impairment (CRCI). CRCI is an important and highly prevalent restriction for cancer patients substantially affecting the patients' individual health-related quality of life (HR-QoL) [1–3].

Driven by early tumor detection, advanced anticancer treatments, and the aging of the world's population, the number of cancer survivors is rising worldwide. In 2018, approximately 43.8 million cancer patients had been diagnosed during the previous 5 years (reference: www.canceratlas.cancer.org) with up to 35% suffering from objective and lasting cognitive decline due to cancer treatment.

The cognitive impairment varies widely among cancer patients regarding onset, severity, duration, and involved cognitive domains. The deficits are usually mild to moderate and often transient. Longitudinal studies showed significant cognitive deficits shortly after chemotherapy followed by partial recovery in the following 6–12 months [4, 5]. In some patients, however, CRCI can last for years or present with more severe or progressive manifestations [1, 6–9]. Notably, CRCI is not limited to older patients, as it is also frequently observed in younger patients [10].

Self-reported cognitive complaints occur in approximately 75% of breast cancer patients during and/or after chemotherapy. However, only 15–35% patients had an objective cognitive decline in neuropsychological testing [7, 11, 12]. The mismatch between subjective complaints and objective cognitive deficits is still debated. Possible reasons for this are relatively mild cognitive symptoms not detected by standardized neuropsychological testing, but other causes of cognitive deficits in cancer patients, such as modern hormone, targeted and immunological therapies, premorbid cognitive reserve and resilience, genetic polymorphisms, cancer treatment-related factors, psychological factors, and systemic inflammation-associated cognitive dysfunction (Fig. 1), also predispose to a higher risk of cognitive impairment [1, 13].

While many chemotherapeutic agents (Fig. 1) are used for cancer treatment, only a few have been studied regarding their effects on cognition and brain functions. Given the diverse biological effector mechanisms of cytotoxic chemotherapies, individual substances mediate distinct effects in the CNS and differ from each other [1, 2]. Furthermore, most clinical trials, neuroimaging and neuropsychological studies were mainly carried out in breast cancer (85%) and only a small number of investigations were performed in colorectal, ovarian, prostate cancer, or lymphoma [1, 2].

The influence of neurotoxic treatment on cognitive function has a deleterious impact on the patients' HR-QoL including autonomy, self-confidence, social relationships (family, friends, social contacts), return to work or school (education), and everyday activities (Fig. 1), especially in the context of long-term cancer care. Therefore, there is a growing demand from cancer patients for CRCI management leading to studies and approaches implementing cognitive behavioral intervention, cognitive rehabilitation, and physical activity in supportive care of cancer patients [14, 15].

Clinical presentation

Incidence and cognitive domains

Some studies demonstrated that estimated 10–30% of cancer patients have already detectable cognitive deficit prior to chemotherapy (pretreatment cognitive impairment). Approximately 30% of patients reported increasing cognitive symptoms with each treatment cycle (early CRCI) and about 75% of cases had significant cognitive impairment shortly after chemotherapy completion lasting up to 6–12 months (posttreatment CRCI). Importantly, about 15–35% of cancer patients experience changes in cognitive performance several months after the completion of treatment (Fig. 1; [4, 5, 15–19]).

Various neuropsychological tests revealed cognitive deficits mainly in the following domains: attention and concentration ability, short-term and working memory, prospective memory, executive functions, reaction and processing speed, verbal fluency, and visual–spatial functioning (Fig. 1; [14, 20, 21]). The patients themselves often report problems staying concentrated and focused (e.g., conversations, daily work), difficulties in memory, executive functions (e.g., time management, decision-making, problem-solving and cognitive flexibility, cognitive control of behavior), word finding, local and chronological orientation.

Pretreatment cognitive impairment

A number of recent studies showed that cognitive impairment and altered behavior in cancer patients manifested prior to chemotherapy is highly prevalent when objectively tested (5–15%) and subjectively self-reported (11–33%) [22–24]. These observations lead to the hypothesis that pretreatment cognitive deficits may be associated with

- the *cancer itself* (e.g., systemic inflammation-associated cognitive dysfunction through proinflammatory mediators created by peripheral tumors and the activated immune system),
- reduced *baseline cognitive resilience and reserve* (e.g., older age, structural and/or functional cortical and subcortical changes due to dementia, leukoencephalopathy, brain metastasis, stroke, multiple sclerosis),
- an *acute or chronic psychological stress reaction* (e.g., sympathetic nervous system activation with secretion of the stress hormones adrenaline, noradrenaline, and cortisol and consecutive activation of the immune system),
- *psychological symptoms* (e.g., psychosocial distress and adjustment disorder, anxiety, depression, fatigue, sleep disorders) [25, 26].

Cognitive alterations and sickness behaviors observed in acute diseases (e.g., infection, trauma) mainly have a protective role diverting energy from cognitive processes and general locomotion to the immune system ("principles of life history theory") [27–29]. However, less is known about cognitive decline and sickness behaviors during chronic noninfectious diseases, in particular cancer, while the classical sickness behaviors associated with cancer (e.g., fatigue, anorexia, and lethargy) are recognized as deleterious symptoms.

CRCI during and after chemotherapy

Only a few longitudinal studies investigated changes in cognition during chemotherapy. It is estimated that approximately 30% (range 13–48%) of cancer patients report increasing deterioration of cognitive functions after each chemotherapy cycle, by as early as the first cycle (*early CRCI*) [30, 31]. Therefore, the mechanism of action of a cytotoxic substance, its opportunity to

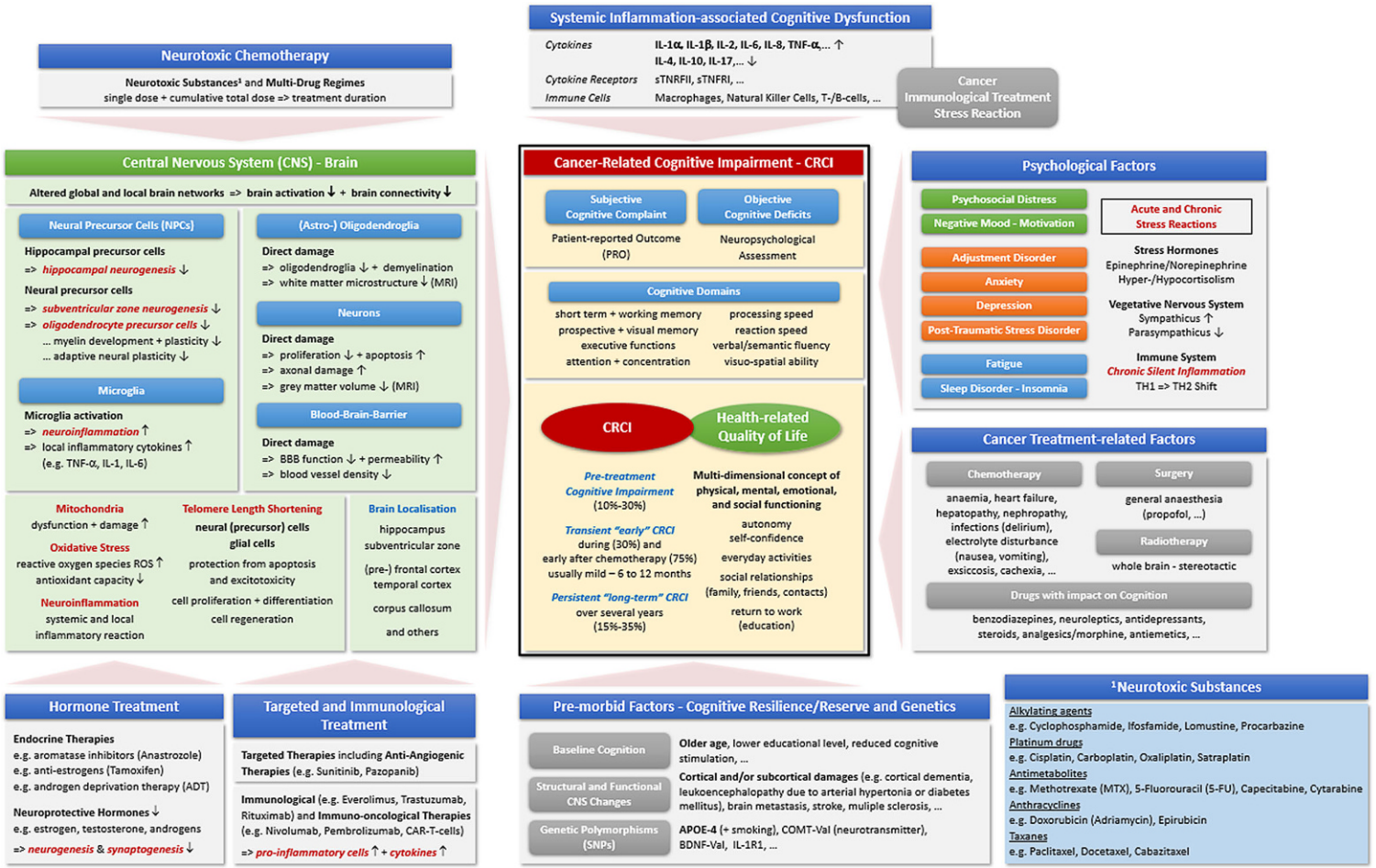

Fig. 1 Schema depicting the complexity of cancer-related cognitive impairment (CRCI). In cancer patients and survivors, neurotoxic chemotherapeutic agents, administered alone or in drug combinations, have a great impact on cognitive functions in different brain areas involved in memory, executive functions, attention/concentration, and processing speed. Cancer treatments are associated with structural and functional changes of the brain such as brain volume reduction, white matter abnormalities, and altered global/local brain network activation. These effects are related to direct cellular toxicity (neuronal/oligodendrocyte precursor cells, neurons, astro-/oligodendroglia) and neuroinflammation (microglia). Importantly, the cognitive performance of cancer patients can also be affected long-term by various aspects including newly developed treatment approaches (hormone, targeted, immunotherapy, and immuno-oncological therapies), cognitive reserve and resilience, genetic polymorphisms, cancer treatment-related factors and in particular psychological factors, highlighting the urgency of specific onco-neuro-psychological patient care. Figure developed and modified from M. Hutterer, M. Zeller: Gibt es ein „ChemoBrain"? neurologisch 04/2018. *APOE* Apolipoprotein E, *BBB* blood–brain barrier, *BDNF* brain-derived neurotrophic factor, *COMT* catechol-O-methyltransferase, *IL* interleukin, *IL-1-R1* interleukin-1-receptor 1, *MRI* magnet resonance imaging, *TNF-α* tumor necrosis factor-alpha, *sTNF-RII* tumor necrosis factor-receptor type II

cross the blood–brain barrier (BBB) into the central nervous system (CNS), the drug dosages (individual single dose, in particular the cumulative total dose and number of cycles), the route of administration (oral, intravenous, subcutaneous) and the duration of treatment of a neurotoxic agent (mainly given in combined chemotherapy regimens) are highly relevant parameters for CNS neurotoxicity [1, 2, 26].

The frequency of cognitive deterioration in cancer patients tested immediately or up to 1 month after chemotherapy completion, compared with baseline or control groups, is estimated to be 75%, but ranged between 17 and 86% in various studies [2]. In this context, please note that the subjectively perceived treatment burden can be an important determinant of self-perceived cognitive functions [4, 5].

Long-term cognitive impairment after chemotherapy

Studies demonstrated that certain chemotherapeutic agents frequently cause long-lasting neurological deficits (e.g., methotrexate; Fig. 1). However, the findings with respect to CRCI at 6 and 12 months after chemotherapy completion are remarkably diverse.

In some reports, cognition performance was still significantly impaired at the same level 6 months after treatment completion compared to pretreatment levels, immediately after chemotherapy treatment completion and/or control groups. Most studies, however, reported a slow and continuous improvement in cognition during the first 12 months after treatment completion, whereas other studies detected further cognitive deterioration in this period [2, 22].

In this context, Wefel et al. [32] found significant cognitive decline in 61% of breast cancer patients 6 months after FAC chemotherapy (fluorouracil, epirubicin, cyclophosphamide). Notably, of these CRCI patients 71% already had cognitive symptoms during or shortly after he chemotherapy, but 29% demonstrated newly developed cognitive dysfunction afterwards. The same group was able to confirm these results in men with nonseminomatous germ cell tumors showing that 52–67% of patients had worsened significantly compared with an examination immediately after chemotherapy [33]. Hermelink et al. [5] reported a significant improvement in cognitive function in 28% of breast cancer patients, whereas 27% patients showed significant cognitive decline.

Summarizing, a number of cancer patients suffer from cognitive impairment 6 months after completion of chemotherapy but seem to recover afterwards in the following months. However, a few patients exhibit a worsening of cognitive symptoms in the further course.

Pathogenesis

In the last few years, a number of clinical trials, neuroimaging and animal studies demonstrated that some chemotherapeutic agents (Fig. 1) have direct neurotoxic effects in particular on neural precursor cells (NPCs) and microglia, but also neurons, astro-/oligodendrocytes and the blood–brain barrier (BBB). These side effects result in functional and structural brain changes with altered global and local brain networks as well as reduced brain activation and connectivity leading to cancer-related cognitive impairment [1, 34, 35].

Impaired neurogenesis and microglial activation

Cancer therapies alter the function of NPCs through depletion of precursor cells and lasting perturbation of the brain microenvironment that regulates NPC function in hippocampus and subventricular zones [36, 37]. Recent work revealed that therapy-induced persistent microglial activation and neuroinflammation is an important microenvironmental factor that limits the function and recovery of NPCs as well as mature neural cells [35, 38–40].

In animal models several chemotherapeutic agents have been shown to be associated with hippocampal cell death and inhibited hippocampal cell proliferation resulting in decreased neurogenesis and thereby loss of hippocampus-dependent cognitive functions with treatment-induced microglial activation as the critical component in the cause of CRCI [41, 42].

Direct neurotoxic effects on brain cells and cell–cell interactions

Furthermore, neurotoxic treatments may also directly injure neurons, astrocytes and oligodendrocytes with subsequent neuronal dysfunction and cell loss (grey matter and hippocampal volume reduction on MRI, cortical hypometabolism on FDG PET), demyelination (white matter changes of subcortical areas and corpus callosum on MRI) and alterations of neurotransmitter levels (e.g., dopamine) [43]. Other studies highlighted the complexity of dysregulated intercellular connections with a deleterious impact of neurotoxic agents on glial–glial and neuron–glial interactions, important for structure, function, and neural plasticity of the CNS [35–40]. These observations might explain delayed and long-term neurotoxic cognitive impairment in cancer survivors [36].

Oxidative stress and mitochondrial dysfunction

Oxidative stress effects are a highly probable mechanism of CRCI pathogenesis on cellular basis, which is mainly caused by an imbalance between ROS (reactive oxygen species, e.g., free radicles and peroxides) production and the biological antioxidant capacity of the brain [43]. ROS products cause DNA mutations with cellular and mitochondrial dysfunction [44] and induce cumulative damage of small blood vessels leading to reduced blood vessel density, brain perfusion

and BBB dysfunction [43]. Based on these findings, several approaches are studying the concomitant use of antioxidant agents as an attempt to attenuate the oxidative stress underlying CRCI.

Cerebrovascular alteration

In clinical and animal studies it has been established that some chemotherapeutic agents reduce cerebral blood flow and perfusion indicating vascular toxicity in particular of small vessels and BBB permeability [45, 46]. Angiogenesis and neurogenesis are closely related [45]. These observations led to the assumption that treatment-associated reduction of cerebral blood vessel density with subsequent depletion of energy and proliferative signals could be an additional contributing cause of hippocampal and brain dysfunction [43].

Factors influencing the development and manifestation of CRCI

Beyond the impact of neurotoxic chemotherapy, several other factors such as modern endocrine, targeted or immunological treatment approaches, premorbid cognitive resilience and reserve, cancer treatment side effects, psychosocial factors and systemic proinflammatory conditions directly interact with various brain functions and cognitive performance [1, 2, 26].

Endocrine therapies

Hormonal receptors are widespread throughout the brain, and endocrine effects are important for brain function. A number of clinical trials in breast and prostate cancer patients as well as animal models reported neuroprotective and antioxidant effects of the hormones estrogen and testosterone [47, 48]. These observations led to the hypothesis that a hormone reduction as part of an endocrine antihormone cancer therapy may induce or increase cognitive deficits [47].

In this context, the influence of the woman's pretreatment hormonal milieu in relation to cognition may be important. Sudden changes in circulating estradiol (e.g., chemotherapy-induced amenorrhea in premenopausal women) may impair the cognitive side effects of antihormonal therapies. Therefore, understanding cognitive decline in breast and prostate cancer patients remains an important research priority, given the large number of long-term survivors [49–51].

Systemic inflammation-associated cognitive impairment

A major contributing reason of cancer-related cognitive impairment is proposed to be a systemic immune activation and dysregulation with the release (e.g., IL-1α, IL-1β, IL-2, IL-6, IL-8, TNF-α, TGF-β) or decrease (e.g., IL-4, IL-10, IL-17) of proinflammatory cytokines and an increase of cytokine receptors (e.g., sTNRFII, sTNFRI). Several causes of this inflammatory response were reported including immune defense reactions (e.g., cancer itself, infections), different cancer treatments (e.g., cytotoxic chemotherapy such as taxanes; immunological therapies such as everolimus, IL-2, interferon-α; immuno-oncology treatments such as nivolumab, pembrolizumab), acute or chronic emotional distress and psychological disorders (e.g., depression, anxiety, posttraumatic stress disorder, fatigue, insomnia) [1, 26].

These proinflammatory mediators exert their effects on cognitive impairment and behavior change through induction of central cytokine release activating microglia and leading to negative effects on neuron precursor cells (neurogenesis), neuron function and synaptic plasticity, neuron–glia and glia–glia interactions, astrocytes (reactive astrocytosis) und oligodendrocytes (changes in oligodendroglial myelination process) [26, 31, 43, 52].

Several studies showed cognitive impairment after cancer diagnosis but before the onset of chemotherapy [5, 19]. On the one hand early cognitive impairment in cancer patients can be attributed to emotional distress following cancer diagnosis, thus, leading to stress-related proinflammatory factors triggering neuroinflammatory cascades in the brain [5, 19, 32, 47, 53]. On the other hand, in animal studies the presence of a tumor itself was accompanied by increased levels of proinflammatory cytokines and reduced brain-derived neurotrophic factor (BDNF) resulting in hippocampal dysfunction, presumably due to the decreased rate of hippocampal neurogenesis [54, 55].

Cognitive reserve and resilience

Another important contributing CRCI risk factor seems to be the cognitive reserve, which is described the premorbid cognitive ability before chemotherapy compared with age-matched normal values. Key factors for lower cognitive reserve are older age, structural and/or functional brain function deterioration, possibly associated with mild cognitive impairment or even cortical/subcortical dementia [1]. Especially among elderly cancer patients, the difficulty of isolated signs and symptoms of pretreatment cognitive impairment regarding older age and cognitive decline induced by cancer treatments is a challenge.

Finally, decreased educational status played an important role in development of CRCI and was linked with decreased mood and depressive symptoms [2, 56].

Genetic predisposition and polymorphisms

In recent studies the potential impact of genetic single nucleotide polymorphisms (SNPs) has been explored.

The gene encoding the protein apolipoprotein E (APOE) was one of the first suspected candidates. The allelic variant APOE-4 is a well-known risk factor for Alzheimer's disease. Studies showed the possession of one or more apolipoprotein APOE-4 alleles, especially in combination with smoking, also contributed to poorer cognitive performance following neurotoxic chemotherapy and/or hormonal therapy in breast cancer patients [1, 57, 58]. The role of neurotransmitter metabolism as a potential genetic risk factor was demonstrated with the enzyme catechol-O-methyl-transferase (COMT, degradation of catecholamines). The SNP COMT rs165599 was correlated with impaired cognitive functions in patients receiving chemotherapy indication that the COMT metabolic pathway may be involved in CRCI [59]. Furthermore, the BDNF polymorphism SNP rs6265 [Val66Met] was implicated to have protective effects in the decreased susceptibility of CRCI in breast cancer patients [60, 61]. Based on the described inflammation-associated cognitive impairment, a protective relationship between the SNP IL1R1 rs2287047 and cognitive complaints was demonstrated in breast cancer survivors. In contrast, the SNP IL1R1 rs949963 was a significant genotypic predictor with breast cancer patients carrying the rare 'A' allele (e.g., GA+AA) having lower perceived attentional function [1, 62], highlighting the complexity of cytokine SNPs.

Cancer treatment-related factors

Chemotherapies can cause several unpleasant side effects also affecting the cancer patients' cognitive performance. Important attendant symptoms are fatigue (feeling of exhaustion), infections (with delirium), anemia, organ dysfunction (e.g., hepatopathy, nephropathy, heart failure), electrolyte disturbance (nausea, vomiting), and cachexia [1, 3].

CRCI is especially severe after (whole brain) cranial radiation with functional (neuroinflammation) and subacute structural (e.g., leukoencephalopathy) brain changes and can have critically influence on the long-term HR-QoL [1].

In addition, several drugs with effects on cognition (e.g., benzodiazepines, neuroleptics, antidepressants, steroids, analgesics/morphine, antiemetics), but also surgery and general anesthesia (e.g., propofol) have to be considered [63].

Finally, rare causes of (common acute) cognitive impairment that need to be addressed in individual cases, include for example tumor-associated paraneoplastic limbic encephalitis, brain metastases and neoplastic meningitis, (opportunistic) pathogen-associated infections (e.g., herpes encephalitis) or status epilepticus.

Psychological factors

Acute and subacute emotional distress reactions (e.g., adjustment disorder, negative mood) are quite common as response to a cancer diagnosis. The somatic stress reaction itself (e.g., the stress hormones adrenaline/noradrenaline and cortisol) but also a subsequent activation of the immune system sustainably alters cognitive brain functions.

Furthermore, subacute and chronic psychological diseases (e.g., depression, anxiety, posttraumatic stress disorder) and other attendant symptoms (e.g., sleep disorders, fatigue) result in a lasting chronic stress condition leading to a (silent) chronic proinflammatory state (e.g., T-cell TH1 to TH2 switch; hypo-/hypercortisolism) and restriction of the patients' cognitive ability [26, 53, 64]. Therefore, an evaluation of these psychological factors within a self-reported or neuropsychological CRCI assessment seems to be absolute necessary.

Conclusion

The neurotoxicity of various chemotherapeutic substances and regimens, respectively, cannot explain all cancer-related cognitive dysfunction observed in cancer patients. Therefore, many of the additional factors mentioned in this article have a critical and concomitant value in the development of cognitive impairment in cancer patients. For this reason, the support from additional staff (e.g., neuropsychologists, clinical psychologists) and more comprehensive studies are needed to understand these relationships.

Patient-reported outcomes and neuropsychological measures

Currently, there is no general consensus on the methodology and time-points for measuring cognitive function in cancer patients and long-term survivors. CRCI was assessed in a range of cancer populations using self-reported assessments (subjective cognitive complaint) and neuropsychological tests (objective cognitive deficits) [1, 3, 9, 32]. But there is still a lack of longitudinal research examining occupationally active cancer survivors.

Self-reported cognitive complaints are clinically very important and usually assessed with patient-reported outcomes (PROs) such as FACT-Cog (time frame 5 min), especially developed to assess cognitive complaints in cancer patients [65].

The minimal clinically important difference (MCID), a patient-centered concept capturing the magnitude of the improvement and also the value patients place on the change, can be used as a screening method to assess cognitive difficulties before any further assessment [66].

Neuropsychological testing provides objective assessments of various cognition domains but is gener-

ally time consuming. Lange et al. [1] gave an overview about neuropsychological methods recommended by the international cancer and cognition task force (ICCTF) [9].

Typically, subjective cognitive complaints and objective performance on neuropsychological tests do not correlate very highly [23, 67]. Cancer patients and long-term survivors often report cognitive problems but score in a normal range on neuropsychological testing. As reasons for this phenomenon are assumed that (i) neuropsychological tests cannot detect relatively subtle cognitive changes experienced by the patient, (ii) psychological factors (e.g., anxiety, depression, fatigue, insomnia) that influence perceived cognitive problems have to be taken into greater account in objective testing, and (iii) anticipation of an outstanding neurotoxic treatment may promote the patient's assumption of chemotherapy's harmfulness, also boosting expectations of cognitive side effects [4, 5, 53, 67–70].

Interestingly, MRI studies also suggested that patients and survivors employ compensatory activation of additional brain regions to maintain performance on neuropsychological tests [69, 70].

CRCI management and treatment

At present there is no effective preventative or regenerative treatment for preserving or restoring brain function during or after chemotherapy. However, several strategies of CRCI management have been studied and consider pharmacological treatment, cognitive behavior interventions, cognitive rehabilitation, and physical activity as supportive (neuro-oncological) treatment approaches.

Pharmacological treatment

Metformin, a commonly used and well-tolerated antihyperglycemic agent, can enhance regenerative properties of the brain through its action on neuronal precursor cells (NPCs; e.g., improved hippocampal neurogenesis), the function of aged oligodendrocyte precursor cells (OPCs; increased OPC differentiation and remyelination) and possibly suppression of microglia-associated neuroinflammation [71–73].

Recently, Ayoub et al. [74] demonstrated that in pediatric brain tumor survivors who had been treated with cranial radiation and chemotherapy, metformin was associated with significant better cognitive performance than placebo (especially declarative and working memory), and structural improvement with increased myelination of white-matter tracts on advanced MRI. In addition, no serious adverse events were reported.

Otherwise, there is no clinical evidence for the effectiveness of other pharmacological agents in randomized controlled trials for CRCI as reported in a recent review [75]. Currently, clinical studies are investigating diverse drugs such as neurostimulants (e.g., methylphenidate [acts similarly to amphetamines], modafinil [increases catecholaminergic signaling]), neuroprotecting antidementing drugs (e.g., donepezil [acetylcholinesterase inhibitor], memantine [NMDA antagonist]) or antineuroinflammatory substances (e.g., metformin) with the objective to prevent or treat CRCI [75]. Furthermore, animal models suggested that fluoxetine and cotinine (main metabolite of nicotine) may improve cognitive performance and emotional state, but further research is required [1].

Cognitive behavior interventions and cognitive training

Cognitive behavioral interventions generally focus on information, education, cognitive behavior therapy, teaching of compensatory strategies, and cognitive training.

A survey conducted in about 1600 cancer survivors (>85% breast cancer patients, median of 3 years after cancer treatment) found that 75% of the participants self-reported cognitive deficits related to cancer treatment [76]. Three-quarter of these patients wished to receive support, particularly cognitive training (72%). Cognitive behavior therapy and cognitive rehabilitation studies (e.g., inpatient and outpatient programs, web-based rehabilitation programs at home) in cancer survivors consistently demonstrated improvement in self-reported cognitive functions but showed variable results for objective testing [77–79].

Unfortunately, many of the studies included few patients and did not have a therapeutic control group making it difficult to determine whether any improvement seen was due to an expectancy effect.

Physical activity

Current data on physical intervention studies showed positive effects of various exercise programs (e.g., aerobic training, yoga, tai-chi) with benefits on self-perceived cognitive functions and objective cognitive complaints, but also a reduction of systemic inflammation responses [80–82]. Additional randomized clinical trials with standardized self-reported and neuropsychological assessments and controlling for potential confounders, respectively, are needed to confirm and expand preliminary findings.

Limitations of CRCI studies

The first major limitation is that about 85% of CRCI studies have focused on breast cancer patients. Otherwise, these patients represent the ideal cohort for clinical research because breast cancer is a common tumor entity, patients usually have few comorbidities (limiting confounders), survival rates allow a longitudinal assessment, and there are various treatment regimens allowing for control groups.

Another important limitation is that a lot of clinical trials do not specify which chemotherapy the patients received. Furthermore, cancer patients with different chemotherapy protocols were frequently included leading to data heterogeneity. In addition, the majority of patients were treated with chemotherapeutic drug combinations of two or more cytotoxic substances, making specific cognitive changes difficult to trace back to a single substance.

In addition, a lack of standardization of subjective self-reported outcome measurements and objective neuropsychological tests, often with lack of information on test sensitivity and specificity with regard to CRCI, and a missing consensus how the collected data should be analyzed and interpreted are other major restrictions in CRCI studies raising clinical trial data heterogeneity. Future investigations should also take into consideration learning or practice effects in the case of repeated neuropsychological tests, in particular if less than 6 months apart.

In addition, most of the currently available neuropsychological tests may not be sensitive enough to detect subtle changes in cognition. Therefore, more research is needed to develop new testing methods and validate these first in healthy patients to establish age-dependent values of the norm. Then their sensitivity should be verified in larger patient cohorts with various types of cognitive impairment.

Conclusion

Cancer-related cognitive impairment (CRCI) is common in cancer patients with an estimated incidence of about 75% at any time during or after treatment. The observed cognitive impairment widely varies with mild to severe manifestations, alteration of various cognitive domains, rapid recovery in some patients or lasting for long periods in others, hence impacting the individual patients' health-related quality of life.

Neurotoxic agents used alone or in drug combinations mainly affect neural and oligodendrocyte precursor cells as well as microglia resulting in impaired neurogenesis and neuroinflammation, neuronal dysfunction and white matter tract demyelination.

Importantly, numerous, simultaneously occurring influence factors (e.g., hormone, targeted, immunological and immune-oncological treatment; cognitive reserve; genetic polymorphisms; cancer treatment-related risk factors; psychological factors) may also have sustainable effects on cognitive functions. Therefore, it is essential to assess CRCI patients for frequent symptom clusters and to treat these symptoms if present.

Validated self-report measures of cognition and standardized neuropsychological tests should be used in clinical routine. However it is necessary to consider that the relatively subtle cognitive changes often experienced by cancer survivors are not detected in traditional neuropsychological tests. Therefore, more sensitive cognitive neuroscience-based assessments with specific subcomponents for cognitive functions are needed for clinical practice. In addition, early detection of cognitive deficits is needed, especially in elderly and high-risk patients, who should be screened for cognitive impairment before and during treatment.

So far, no pharmacological agents have been approved to prevent or improve CRCI. The most promising treatment strategy seems to be cognitive behavioral intervention and cognitive rehabilitation and possibly physical activity programs, but its impact on improvement in daily function remain unclear.

Therefore, more studies and robust clinical trials are needed to investigate effective strategies of CRCI management in routine oncology supportive care to improve the individual health-related quality of life of cancer patients and survivors.

Take home message

Cancer-related cognitive impairment (CRCI) is multicausal and not limited to neurotoxic substances alone. Thus, in clinical routine and CRCI management, endocrine, targeted, and immunological treatments, the premorbid individual cognitive resilience/reserve, genetic polymorphisms, cancer treatment-associated factors, and psychological factors must always be considered.

Conflict of interest M. Hutterer and S. Oberndorfer declare that they have no competing interests.

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