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REVIEW

Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors

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Background: Advances in diagnostic and therapeutic strategies in oncology have significantly increased the chance of survival of cancer patients, even those with metastatic disease. However, cancer-related cognitive impairment (CRCI) is frequently reported in patients treated for non-central nervous system cancers, particularly during and after chemotherapy.

Design: This review provides an update of the state of the art based on PubMed searches between 2012 and March 2019 on 'cognition', 'cancer', 'antineoplastic agents' or 'chemotherapy'. It includes the most recent clinical, imaging and pre-clinical data and reports management strategies of CRCI.

Results: Evidence obtained primarily from studies on breast cancer patients highlight memory, processing speed, attention and executive functions as the most cognitive domains impaired post-chemotherapy. Recent investigations established that other cancer treatments, such as hormone therapies and targeted therapies, can also induce cognitive deficits. Knowledge regarding predisposing factors, biological markers or brain functions associated with CRCI has improved. Factors such as age and genetic polymorphisms of *apolipoprotein E, catechol-O-methyltransferase* and *BDNF* may predispose individuals to a higher risk of cognitive impairment. Poor performance on neuropsychological tests were associated with volume reduction in grey matter, less connectivity and activation after chemotherapy. In animals, hippocampus-based memory and executive functions, mediated by the frontal lobes, were shown to be particularly susceptible to the effects of chemotherapy. It involves altered neurogenesis, mitochondrial dysfunction or brain cytokine response. An important next step is to identify strategies for managing cognitive difficulties, with primary studies to assess cognitive training and physical exercise regimens.

Conclusions: CRCI is not limited to chemotherapy. A multidisciplinary approach has improved our knowledge of the complex mechanisms involved. Nowadays, studies evaluating cognitive rehabilitation programmes are encouraged to help patients cope with cognitive difficulties and improve quality of life during and after cancer.

Key words: cancer-related cognitive impairment, cancer treatments, cancer patients, animal model, neuro-imaging, managementof cognitive impairment

Introduction

Patients with non-central nervous system (CNS) cancers report cognitive symptoms, also called 'cancer-related cognitive impairment' (CRCI), mainly studied after chemotherapy, such as impairment of short-term and working memory, attention, executive functions and/or processing speed [1–4]. Cognitive complaints are reported by ≥50% of breast cancer patients after chemotherapy; however, only 15%–25% have objective cognitive decline [2, 5]. The relation between objective and subjective troubles is still debated and complaints are often linked with psychological factors [6]. State-of-the-art updates were published in 2011 and 2015 by the International Cancer and Cognition Task Force (ICCTF) [1, 4], primarily focussing on neuropsychological tests and clinical data with chemotherapy. Since then, a growing body of literature has highlighted the potential effects of other cancer treatments and pathophysiological mechanisms.

New generations of hormone therapies, targeted therapies, and immunotherapy have resulted in improved survival rates for some patients with, however, potential impact on cognition [7, 8]. Consequently, the long-term toxic impact of treatment on neurological function is an important issue in terms of quality of life (QoL).

Despite recent large cohort studies utilizing neuropsychological testing and brain imaging in cancer patients treated mainly with chemotherapy, it remains uncertain whether cognitive deficits result from the treatment, the cancer itself, and/or psychological factors. Moreover, studies have suggested that factors such as age, genetic polymorphisms, and psycho-social components may predispose to a higher risk of cognitive impairment.

To better understand the pathophysiology of CRCI and the direct impact of different cancer treatments, animal models have been developed [9]. Animal studies allow for the investigation of selective and combined effects of the disease and treatment on neurocognitive function, the influence of parameters such as stress, mood and aging on cognitive impairment, and for the development of rehabilitation strategies. Brain imaging can also help document mechanisms involved in CRCI, as shown by recent studies [3, 10, 11].

As cognitive difficulties have a negative impact on QoL (autonomy, return to work, social relationships, and self-confidence) in the context of long-term cancer care, there is a growing demand from patients for CRCI management. This has led to studies implementing cognitive rehabilitation in cancer patients.

This review presents an update on CRCI in non-CNS cancers, taking into consideration the increasing use of newer anticancer therapies and the development of multidisciplinary (pre-clinical, imaging) and interventional (management) research strategies.

Search strategy and selection criteria

References are from searches of PubMed between 2012 and March 2019. The terms 'cognition' [MeSH Terms] or 'cognition disorders' [MeSH Terms], 'cancer', 'antineoplastic agents' [MeSH Terms], or 'chemotherapy' were used. Keywords including 'cancer' and 'brain' or 'cerebral' or 'central nervous system' and 'cognition' and 'animal' or 'mouse' or 'rat' were used for animal models. We also searched reference lists of identified articles for other relevant reports. Articles related to CNS cancers, childhood cancers, editorials, reviews (except systematic reviews and meta-analyses, and the four recent reviews of the ICCTF), feasibility, and pilot studies or studies with less than 50 patients were excluded. The final reference list was generated based on relevance to the topics covered in this review.

Detecting CRCI in cancer patients

Patient cognitive complaints are clinically important, but neuropsychological testing provides objective assessments of various domains of cognition. The literature indicates that there is considerable variability regarding the severity, duration, or alteration of cognitive domains. The ICCTF [4] recommends using the following criteria for determining cognitive impairment: ≥2 test scores ≤−1.5 standard deviations from the normative mean (or an appropriate control group) or one test score ≤−2.0 standard deviations. Importantly, the more tests administered, the higher the probability of finding cognitive impairment. Ingraham and Aiken [12] provide probability curves and a statistical approach to determine whether the observed frequency of cognitive impairment exceeds the expected rate based upon the number of tests administered.

Cognitive complaints are usually assessed with PROs such as FACT-Cog (time frame: 5 min), especially developed to assess cognitive complaints in cancer patients. To help clinicians and researchers to detect significant complaints, minimal clinically important difference (MCID) can be used [13, 14]. It could be also used as a screening method to assess cognitive difficulties before any further assessments and treatment strategy.

Cognitive complaints and performance on neuropsychological tests often do not correlate very highly [15]; survivors often report cognitive problems but score in the normal range on neuropsychological testing. This pattern is often attributed to psychological factors such as anxiety, depression [15, 16], fatigue, or insomnia [17] that influence perceived cognitive problems to a greater degree than performance on objective testing [18] enhancing the importance of assessing these factors [16]. Imaging studies also suggest that survivors employ compensatory activation of additional brain regions to maintain performance on neuropsychological tests [19, 20]. Therefore, survivors' perception may be correct: cognitive functioning is affected in day-to-day life, but compensatory mechanisms maintains performance in the structured, distraction-free environment of neuropsychological testing. Finally, this lack of association may be related to concerns about the sensitivity and specificity of traditional neuropsychological tests to detect the relatively subtle cognitive changes experienced by cancer survivors.

The failure to use of a criterion as described above, heterogeneity of study design and lack of consistency of cognitive measures utilized has led to variability in results and interpretations across studies [4, 21, 22]. ICTTF recommend using cognitive tests with adequate sensitivity to assess the cognitive domains most impaired by cancer treatments (Table 1).

Table 1. Neuropsychological measures recommended by the international cancer and cognition task force (ICCTF) [4]

Main measures	Administration time (min)	Domains assessed
Hopkins Verbal Learning Test-Revised (HVLT-R)	10	Verbal memory and delayed recall
Controlled Oral Word Association Test (COWA)	5	Speeded lexical fluency and executive function
Trail Making Test (TMT)	7	Psychomotor speed and executive function
Additional measures		**Domains assessed**
Auditory Consonant Trigrams	7	Working memory,[a] executive function, complex attention
Letter-Number Sequencing (WAIS)	4	
Paced Auditory Serial Addition Test (PASAT)	15	
Brief test of attention	10	

[a]Investigators are encouraged to supplement the core battery with additional tests of working memory capacity, based on their own preferences.
WAIS, Wechsler Adult Intelligence Scale.

Effect of cancer treatments on cognitive functions

Effect of chemotherapy

Clinical studies. Several studies, mainly in breast cancer but also colorectal, ovarian cancer, and lymphoma, show the impact of chemotherapy on objective cognitive functioning (Table 2) [23, 25, 26]. According to a meta-analysis, CRCI may be related to the duration of treatment with chemotherapy [22]. These cognitive impairments are usually mild to moderate and are often transient. Indeed, a longitudinal study showed a significant cognitive decrease shortly after chemotherapy in breast cancer patients followed by partial recovery 1 year after this treatment in some patients [23].

Memory, processing speed, attention, and executive functions are the domains most impaired post-chemotherapy [1, 4, 21–24]. In addition to objective cognitive impairment, subjective cognitive complaints are one of the major side-effects reported by patients [31] (especially in breast cancer patients) and suggest a temporary negative effect of chemotherapy on cognition. Breast cancer patients treated with chemotherapy had more cognitive complaints, particularly memory and executive functions (1/5 of patients) [6], and reported more cognitive difficulties than before treatment (45.2% versus 10.4%) [29]. However, heterogeneous trajectories of cognitive complaints exist in breast cancer survivors [17]. Furthermore, according to a long-term follow-up study (7–9 years post-surgery), breast cancer survivors treated with systemic treatment did not have more cognitive complaints than those who did not receive treatment [28].

Colorectal patients treated with chemotherapy had also more cognitive complaints particularly at 6 months than patients without chemotherapy (32% versus 16%) [24]. In a small sample of colorectal cancer patients, CRCI had an impact on patient's QoL, but cognitive impairment did not seem to influence patients' relationships and their functional roles [30].

Animal models. Animal model research has been instrumental in validating CRCI as a legitimate medical condition in cancer survivors who receive chemotherapy. In line with the clinical literature, numerous studies involving rodents, tested on a wide range of behavioural tasks, have confirmed that commonly used anticancer drugs produce moderately severe, and often long-lasting, cognitive deficits [32–37]. Memory loss induced by chemotherapy is related to hippocampal and frontal lobes dysfunction and is often reported with attention, working memory, and strategic learning deficits [9, 38].

Animal research has helped to identify critical biological mechanisms that account for CRCI. Indeed, cyclophosphamide, doxorubicin, and 5-fluorouracil prevent the production of new cells in the hippocampus, and suppression of neurogenesis is directly related to accompanying loss of hippocampus-dependent cognitive functions [32, 39]. Furthermore, mitochondrial dysfunction [40] and dysregulation of cytokine activity contribute to at least some of the cognitive deficits seen after chemotherapy. Particular attention has focussed on increased levels of chemotherapy-induced pro-inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α, IL-10) which, in cancer patients, have been related to impairment, especially on tests of frontal lobe function [41, 42].

Impact of other oncological therapies and new treatment strategies in clinical studies and animal models

Beyond the impact of chemotherapy, hormone therapies and targeted therapies, such as antiangiogenics, can induce cognitive deficits (Tables 3 and 4).

Although the results of clinical studies generally are inconclusive, CRCI has been shown with aromatase inhibitors [1]. Breast cancer patients treated with anastrozole had lower executive function scores than healthy controls up to 18 months after the start of treatment [45]. In the same study, women receiving anastrozole alone exhibited deterioration in working memory and concentration 12–18 months after initiation of therapy. Nevertheless, another study did not show a significant difference on cognitive scores post-hormone therapy initiation (tamoxifen or aromatase inhibitors) compared with patients without hormone therapy [27]. Nevertheless, cognitive complaints increased in patients with hormone therapy. More recently, in breast cancer

Table 2. Cognitive impairment induced by chemotherapy in patients

Study	Study design Country	Patients, control group Age	Cognitive assessment	Main CT type (% of patients)	Cognitive measures	Other measures	Statistical analysis	Main outcome
Objective cognition (neuropsychological tests)								
Collins et al. [23]	Longitudinal Canada	Breast cancer (*n*=56, 52 years old ±7.8) versus HC (*n*=56)	Before, shortly and 1 year post-CT	FEC-T: 70%	Digit-symbol coding, symbol search, TMT, digit span, letter-number sequencing, PASAT, Auditory consonant trigrams, COWA, BVMT, HVLT and CNS-Vital signs tests	BDI, POMS	Multilevel growth modelling (controlled for age, education, baseline BDI score) and SRB scores	Significant rate of decline to baseline from 1 year post-CT in patients. 48% of patients had decreased shortly post-CT (9% HC). Significant rebound from short-term and 1 year post-CT
Vardy et al. [24]	Longitudinal Canada and Australia	Colorectal cancer with CT (*n*=173, 57 years old [23–75]), without (*n*=116), or metastatic (*n*=73) versus HC (*n*=72)	Before and 6, 12 and 24 months after CT	Oxiplatin: 42% FU: 31%	Standard cognitive tests, CANTAB, six elements test	FACT-Cog, FACT-G, FACT-F, GHQ	Linear mixed models	Patients with colorectal cancer: more cognitive impairment at each time than HC. No significant added effect of CT Patients with CT: more cognitive complaints at 6 months than patients without CT (32 versus 16%)
Wouters et al. [25]	Cross-sectional The Netherlands	Lymphoma (*n*=106, 47 years old ±12.6) versus HC (*n*=53)	After CT (median months since completion: 54.5)	CHOP/MOPP-ABV : 76%	Stroop, verbal fluency, digit symbol substitution, TMT, WMS visual memory, verbal learning and memory test, finger tapping, Eriksen task	HSCL, EORTC QLQ-C30	Regressions analysis and Ingraham and Aiken probability curves	Patients: cognitive impairment in 16% (with lower education and pre-morbid IQ)
Hess et al. [26]	LongitudinalUSA	Ovarian cancer (*n*=231, 40–79 years old)	Before CT, before cycle 4, after cycle 6, and 6 months after completion of primary CT	NK	HeadMinder Clinical Research Tool (processing speed, motor reaction time, attention)	PAF, FACT-O, FACT-Ntx, HADS	Cognitive impairment: ≥2 cognitive domain impaired at each time based on reliable cognitive index	At cycle 4: 25% of patients had cognitive impairment in at least one domain, 21% and 18% at cycle 6 and 6 months post-CT, respectively

Continued

Table 2. *Continued*

Study	Study design Country	Patients, control group Age	Cognitive assessment	Main CT type (% of patients)	Cognitive measures	Other measures	Statistical analysis	Main outcome
Cognitive complaints (self-report questionnaire)								
Ganz et al. [27]	Longitudinal (baseline data only) USA	Breast cancer (n=189, 52 years old)	Before HT and after CT±RT	Anthracycline: 25%	PAOFI (cognitive complaints), CVLT, WMS, BVMT, ROCF, digit symbol, TMT, Stroop, letter-number sequencing, grooved pegboard	BDI, MFSI WTAR	Multivariable regression models (age and IQ controlled)	1/5 patients had higher memory and/or executive complaints related to CT+RT
Amidi et al. [28]	Longitudinal (only 7–9 follow-up) Denmark	Breast cancer after systemic treatment (n=1503, 63 years old ±8.2) versus without systemic treatment (n=386)	7–9 year follow-up after primary surgery	Mainly CEF and CMF	CFQ	None	ANOVAs and ANCOVA (menopausal status, sociodemographic and clinical covariates)	No significant difference between the two groups
Janelsins et al. [29]	Longitudinal USA	Breast cancer with CT (n=581, 53 years old ± 0.4) versus HC (n=364)	Before and after CT and at 6 months	Anthracycline: 48%	FACT-Cog	WRAT, STAI	Linear mixed model (age, education, race, menopausal status, reading ability, anxiety and depression controlled)	Patients: significant increase of cognitive complaints after CT (45.2 versus 10.4%) and 6 months after CT (36.5% versus 13.6%)
Ng et al. [17]	Longitudinal Singapore	Breast cancer (n=166, 51 years old ± 9.2)	Before CT, 6, 12 and 15 months post-CT initiation	Anthracycline: 65%	FACT-Cog, Headminder	BAI, BFI, EORTC QLQ-C30	Linear mixed model (age, anxiety, fatigue, CT regimen, insomnia, menopausal status, years of education)	5 distinct cognitive trajectories were established
Impact of cognitive dysfunctions								
Galica et al. [30]	Cross-sectional Canada and Australia	Colorectal cancer (n=74, age not known)	Pre- or post-CT or post-surgery	5-FU and oxaliplatin : 52%	CANTAB	Psychosocial Adjustment to Illness Scale–Self-Report (PAIS-SR)	Regression model	Cognitive changes do not influence patients' relationships and functional roles

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Table 2. *Continued*

Study	Study design Country	Patients, control group Age	Cognitive assessment	Main CT type (% of patients)	Cognitive measures	Other measures	Statistical analysis	Main outcome
Pereira et al. [31]	Longitudinal Portugal	Breast cancer (n=506, 55 years old ±11.2)	Before any treatment (including surgery) and 1 year	5-FU, epirubicin, cyclophosphamide, docetaxel: 59%	MoCA	Neurological complications	Cumulative incidence estimates with corresponding 95% confidence intervals	Cognitive decline: frequent side-effect Cognitive decline during the first year after diagnosis: 8.1%

5-FU, 5-fluorouracil; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BVMT, Brief Visuospatial Memory Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; CEF, cyclophosphamide, epirubicin, and fluorouracil; CFQ, Cognitive Failures Questionnaire; CHOP, doxorubicin, cyclophosphamide, vincristine, prednisone; CMF, cyclophosphamide, methotrexate, and fluorouracil; COWA, Controlled Oral Word Association Test; CT, chemotherapy; CVLT, California Verbal Learning Test; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT- (O; Ntx; G; F; Cog), Functional Assessment of Cancer Therapy (Ovarian cancer; Neurotoxicity; General; Fatigue; Cognitive Function); FEC-T, FEC plus taxotere; FU, fluorouracil or capecitabine; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; HSCL, Hopkins Symptoms Checklist; HT, hormone therapy; HVLT, Hopkins Verbal Learning Test; MFSI, Multidimensional Fatigue Symptom Inventory; MoCA, Montreal Cognitive Assessment; MOPP-ABV, mechlorethamine, oncovin, procarbazine, prednisone-doxorubicin, bleomycin, vinblastine; PAF, patients' perceptions of their own cognitive function; PAOFI, Patient's Assessment of Own Functioning Inventory; PASAT, Paced Auditory Serial Addition Task; POMS, Profile of Mood States; ROCF, Rey Osterreith Complex Figure; RT, radiotherapy; SRB, Standardized Regression-Based; STAI, Spielberger State-Trait Anxiety Inventory; TMT, Trail Making Test; WMS, Wechsler Memory Scale; WRAT, Wide Range Achievement Test; WTAR, Wechsler Test of Adult Reading.

patients treated with hormone therapy, no detrimental effect was described at 6-years follow-up [48]. Two studies [44, 46] compared the effects of antiestrogens and aromatase inhibitors on cognition. Both found no significant difference on objective cognitive scores. After randomization for hormone therapy, there was no difference between breast cancer patients treated with aromatase inhibitors or tamoxifen at 6 months and 1-year follow-up [48]. Conversely, cognitive complaints (attention/concentration) significantly increased in tamoxifen users but not in women on exemestane [43].

Ovarian function suppression may also increase cognitive complaints in breast cancer patients but without significant impact on objective cognitive functions [47].

In prostate cancer, the impact of androgen deprivation therapy (ADT) has also been assessed. Overall, little effect on cognition was found (effect size, $g = -0.67$) and, according to a meta-analysis, visuomotor functions are likely the most impaired domain [53]. On the Mini Mental State Examination (MMSE), prostate cancer patients treated with luteinizing hormone-releasing hormone (LH-RH) analogues did not score statistically differently than patients without LH-RH [49]. Otherwise, according to cognitive tests, 20% of patients had cognitive decline 6 months after the start of LH-RH analogues, a majority deteriorating only on one test, without alteration in one domain in particular [51]. Also, patients with ADT had more CRCI, 6 and 12 months after the start of treatment, compared with patients without ADT and healthy controls, but there was no difference between groups in changes of mean-level cognitive performance [50]. Results at 3 months indicate that more prostate cancer patients receiving enzalutamide experienced cognitive complaints than patients taking acetate abiraterone and prednisone [52].

Initial results with targeted therapies suggested an impact on cognition in a subgroup of patients [7]. Cognitive decline was observed after antiangiogenic therapies (AAT), independently of fatigue, in 31% of metastatic renal cell carcinoma patients, the majority of whom did not have cognitive impairment before treatment [7]. In agreement, one study tested the effects of the mTOR inhibitor everolimus in mouse brain functions [54]. No alteration was found in cognitive performance, associated with the absence of modification in hippocampal neural cell proliferation, but weight loss and modification of neural activity in brain areas involved in the sleep/wake cycle suggest AAT-evoked fatigue [7].

Although there are no clinical data on the impact of immunotherapy on cognition, some data are starting to emerge from animal model research. Radiotherapy combined with immunotherapy (checkpoint inhibitor and anti-CTL4 antibody) in an animal model showed behavioural and cognitive altered performances associated with proinflammatory cytokines [55].

Associated psychological, sociodemographic and genetic factors involved in CRCI

Many factors increase risk for CRCI (Figure 1), including psychological and sociodemographic variables and genetic predisposition.

Table 3. Cognitive impairment induced by medical oncology treatments other than chemotherapy in patients

Study	Study design Country	Patients, control group Age	Cognitive assessment	Cognitive measures	Other measures	Statistical analysis	Main outcomes
Hormone therapy—breast cancer							
Schilder et al. [43]	Randomized Longitudinal The Netherlands	Breast cancer, tamoxifen users (n=80, 69 years old ±7.6), exemestane users (n=99, 68 years old ±6.8) versus HC (n=120)	Before and after 1 year of HT (CT naïve)	CFQ and interview questions about cognitive complaints	Cognitive tests (only to assess the relation with cognitive complaints), HSCL, fatigue subscale (EORTC-QLQ-C30), FACT-B-ES	ANOVA, ANCOVA and logistic regressions (anxiety, depression covariates)	In tamoxifen users: increased attention/concentration complaints (not in exemestane users)
Danhauer et al. [44]	Randomized Longitudinal USA	Breast cancer (n=1479, 67 years old ±4.3), tamoxifen and raloxifen groups (randomized)	Baseline, 2 and 3 years follow-up	3MSE, PMA vocabulary, verbal fluencies, BVRT, CVLT, digit span, card rotations, finger tapping	PANAS, GDS	Linear mixed models for repeated measures	No significant interactions between treatment and any of the cognitive test results
Ganz et al. [27]	Longitudinal USA	Breast cancer with HT (n=122, 52 years old ±7.9, tamoxifen or aromatase inhibitor) versus without (n=51)	Before HT and 6 months later	WTAR, CVLT, WMS, BVMT, ROCF, block design, digit symbol, TMT, Stroop, letter-number sequencing, grooved pegboard	PAOFI, BDI, SF-36	Bivariate analyses and multivariable linear regression models	Cognitive complaints (language and communication) increase in HT patients but no significant changes in cognitive scores
Bender et al. [45]	Longitudinal USA	Breast cancer with CT and anastrozole (n=114, 59 years old ± 5.5) versus anastrozole alone (n=173) versus HC (n=110)	Before, 6, 12, and 18 months after the start of HT	CANTAB, digit vigilance, rivermead story, ROCF, RAVLT, verbal fluency, Stroop, grooved pegboard, digit symbol substitution, NART	BDI, POMS	Linear mixed effects modelling (age and estimated verbal intelligence controlled)	Patients with anastrozole (±CT): poorer executive function from before treatment initiation to 18 months than HC and decreased on visual working memory and concentration at 6 months Patients with anastrazole alone: second deterioration in working memory and concentration at 12 and 18 months
Le Rhun et al. [46]	Randomized Longitudinal France	Breast cancer (n=74, 61 years old [49–69]), with tamoxifen (n=37) versus AI (n=37)	Before, 6 and 12 months after the start of HT	MMSE, RAVLT, BVRT, digit and spatial span, TMT, Stroop, verbal fluency, Wisconsin card sorting test	CDS, IADL, EORTC QLQ-C30, HADS	Mixed design analysis models of variance (adjusted for baseline performance)	No significant difference between groups on cognitive scores for all the follow-up
Phillips et al. [47]	Randomized Longitudinal International	Breast cancer with ovarian function suppression + tamoxifen or exemestane (n=54, 44 years old) versus tamoxifen alone (n=20, 46 years old)	Before HT and 1 year later	CogState (seven tasks)	CFQ, GHQ, Brief fatigue inventory	Wilcoxon rank-sum tests to compare the change between the t groups (CT treatment and baseline characteristics controlled)	No significant difference in the changes of objective cognitive scores between all groups

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Table 3. *Continued*

Study	Study design Country	Patients, control group Age	Cognitive assessment	Cognitive measures	Other measures	Statistical analysis	Main outcomes
Van Dyk et al. [48]	Longitudinal USA	Breast cancer with HT (*n*=126, 52 years old ±7.9) versus without (*n*=63, 52 years old ± 9.2)	Before, 6 and 12 months and 3–6 years after the start of HT	CVLT, BVMT, Digit span, coding, letter-number sequencing, PASAT, ROCF, block design, TMT, Verbal fluency, Grooved pegboard, Stroop	BDI, State Anxiety Inventory, WTAR	Linear mixed effect models for repeated measures, analysis of covariance and binary logistic regression	No detrimental effect of HT on cognition
Androgen deprivation therapy—prostate cancer							
Wiechno et al. [49]	Cross-sectional Poland	Prostate cancer with ADT (*n*=88, 67 years old [50–80]) and without (*n*=61)	After RT and LH-RH analogue	MMSE	HADS, questions on QoL	Mann–Whitney and Kruskal–Wallis non-parametric tests	No significant difference between groups for MMSE
Gonzalez et al. [50]	LongitudinalUSA	Prostate cancer with ADT (*n*=58, 67 years old ±8.9 versus without (*n*=84) and HC (*n*=88)	Before, 6 and 12 months after the start of ADT	HVLT, WMS logical memory, digit and spatial spans, BVMT, colour trails, COWA, NART	TIADL	Mixed models and logistic regressions	Patients with ADT: more cognitive impairment at 6 and 12 months No differences between groups in changes in mean-level performance
Morote et al. [51]	Longitudinal Spain	Prostate cancer (*n*=308, 71 years old ±8.1)	Before and 6 months after the start of LHRH analogues	Digit span, visual memory, judgment of line orientation and mental rotation tests, matrix reasoning test	None	Changes outside the baseline 95% confidence intervals were considered significant	20% of patients had significant decline on ≥1 test
Thiery-Vuillemin [52]	Longitudinal International	Prostate cancer with AAP (*n*=46, 73 years old [53–90]) versus ENZ (*n*=59, 76 years old [60–92])	1, 2, and 3 months	FACT-Cog	EORTC QLQ-C30, BFI-SF, BPI-SF	Multivariate repeated measures logistic models and clinically meaningful change	More cognitive complaints in patients with ENZ than AAP and higher risk to develop depression
Antiangiogenic							
Joly et al. [7]	Longitudinal France	Renal cancer (*n*=75, 65 years old [28–81])	Before, 3 and 6 months after the start of AATs	Grober–Buschke test, ROCF, arithmetic, digit-span, letter-number sequencing, TMT, verbal fluencies	MFI, FACT-G and FKSI, BDI, STAI	Fisher's exact test, Wilcoxon test, and Spearman correlation coefficient	Cognitive decline in one-third of patients post-AATs independently of fatigue

AAP, Abiraterone Acetate plus Prednisone; AATs, antiangiogenic therapies; AI, Aromatase inhibitors; ADT, Androgen Deprivation Therapy; BDI, Beck Depression Inventory; BFI-SF, Brief Fatigue Inventory-Short Form; BPI-SF, Brief Pain Inventory-Short Form; BVMT, Brief Visuospatial Memory Test; BVRT, Benton Visual Retention Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; CDS, cognitive difficulties scale; CFQ, Cognitive Failures Questionnaire; CT, chemotherapy; CVLT, California Verbal Learning Test; ENZ, Enzalutamide; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT- (B-ES; G; FKSI), Functional Assessment of Cancer Therapy (Breast-Endocrine Subscale; General; Kidney Symptom Index); GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; HSCL, Hopkins Symptoms Checklist; HT, hormone therapy; QoL, quality of life; LHRH, luteinizing hormone-releasing hormone; MFI, Multidimensional Fatigue Inventory; MMSE, Mini Mental State Examination; NART, National Adult Reading; PANAS, positive and negative affect schedule; PASAT, Paced Auditory Serial Addition Task; PMA, primary mental abilities vocabulary test; PAOFI, Patient's Assessment of Own Functioning Inventory; POMS, Profile of Mood States; ROCF, Rey Osterreith Complex Figure; RT, radiotherapy; STAI, Spielberger State-Trait Anxiety Inventory; TIADL, Instrumental Activities of Daily Living Test; TMT, Trail Making Test; WMS, Wechsler Memory Scale; WTAR, Wechsler Test of Adult Reading.

Table 4. Suspected mechanisms involved in cognitive impairment induced by cancer treatments

Cancer treatments Main studied drugs	Brain functions (excluding complaints)	Suspected mechanisms
Chemotherapy Doxorubicin Taxol Methotrexate Fluorouracil	Clinical studies: memory, processing speed, attention, executive function Animal: working memory, attention, learning	• Diminution of neurogenesis • Disruption of myelin and of oligodendrocyte precursors • Mitochondrial dysfunction • Increased peripheral and brain cytokine production
Hormone therapies Aromatase inhibitors Antiestrogen Androgen deprivation therapy	Clinical studies: executive functions, working memory, concentration (Anastrozole), visuomotor functions	• Linked to endocrine disorders, hypothalamo-pituitary-adrenal axis
Targeted therapies Antiangiogenic therapy	Clinical studies: fatigue, one main domain of cognition in a subpopulation of patients, working memory	• Increased plasma VEGF (fatigue) • Leukoencephalopathy • Inhibition of long-term potentiation
Immunotherapy CTLA-4 Anti-PDL-1	Clinical studies: headaches, encephalopathy, fatigue, and meningitis or hypophysitis with endocrine disorders Animal: executive functions	• Brain microglial activation • Increased peripheral inflammatory cytokines crossing the BBB

VEGF, vascular endothelial growth factor; BBB, blood–brain barrier.

Fatigue, psychological and socio-demographic factors

Anxiety, depression, and fatigue are frequent in cancer patients and should be taken into account for cognitive assessment. Several studies showed an association between cognitive complaints and anxiety [15, 16, 24, 29, 43, 56–59], depression [6, 15, 16, 24, 29, 43, 44, 57, 58, 60], post-traumatic stress disorder symptoms [58], negative affect (e.g. distress and negative mood) [44] and motivation [61].

Fatigue was also frequently associated with CRCI [24, 43, 57–59] and insomnia [17]. Risk factors for these difficulties included education level [25, 58], premorbid intelligence [25, 62], or cognitive reserve [29, 63]. Patient information about cognitive side-effects associated with cancer treatments could induce cognitive complaints [64, 65].

Aging

Although aging is a risk factor for cancer and cognitive impairment, and despite the potential impact of these impairments on patient's autonomy, few studies have focussed on CRCI in cancer patients over 60–65 years old [61, 66–73]. Although several studies showed an impact of age on CRCI, others did not support age as a risk factor. Until now, it is not proved that cancer and/or its treatments (particularly hormone-therapy) induce Alzheimer disease [74]. However, ADT may increase the risk of dementia [75]. Among elderly cancer patients, the difficulty of isolated early signs and symptoms of dementia in relation with the age and cognitive decline induced by cancer treatments is an issue.

Using a cognitive screening tool, a prospective cohort in older patients with breast or colorectal cancer did not show cognitive decline to be associated with chemotherapy [76]. Nevertheless, an interaction was found between age and chemotherapy treatment on memory functioning [66]. Furthermore, in breast cancer patients $\geq$65 years old, 49% had objective cognitive decline after adjuvant treatment [72] a higher proportion than that reported in younger patients. Among patients with decline, 12% of patients had a non-pathological decline, 31% without initial cognitive impairment developed impairment, and 6% experienced accelerated cognitive decline [71]. Furthermore, the oldest patients were more likely to have cognitive decline with chemotherapy, particularly with docetaxel [72]. Chemotherapy in cancer patients 60–64 years old seemed to be associated with faster memory decline compared with older patients treated with chemotherapy, patients without chemotherapy and healthy controls [73]. In addition, results suggest a significant association between measures of biological aging and cognition in breast cancer survivors [77].

Markers, genetic predisposition/polymorphism

Biomarkers of cognitive decline post-cancer treatment, and/or risk factors such as inflammatory status or predisposing genetic factors have been investigated recently [78]. Results on correlations between levels of cytokines or inflammation [79, 80], neurobiological status and genetic polymorphisms are conflicting. However, the most reliable biomarkers associated with CRCI were cytokines (IL-6, TNF-α, etc.), cytokine receptors (sTNRFII, sTNFRI, etc.) and inflammation components [41, 42, 57, 81–83], while mitochondrial DNA content in peripheral blood can be specifically associated with fatigue during chemotherapy [84].

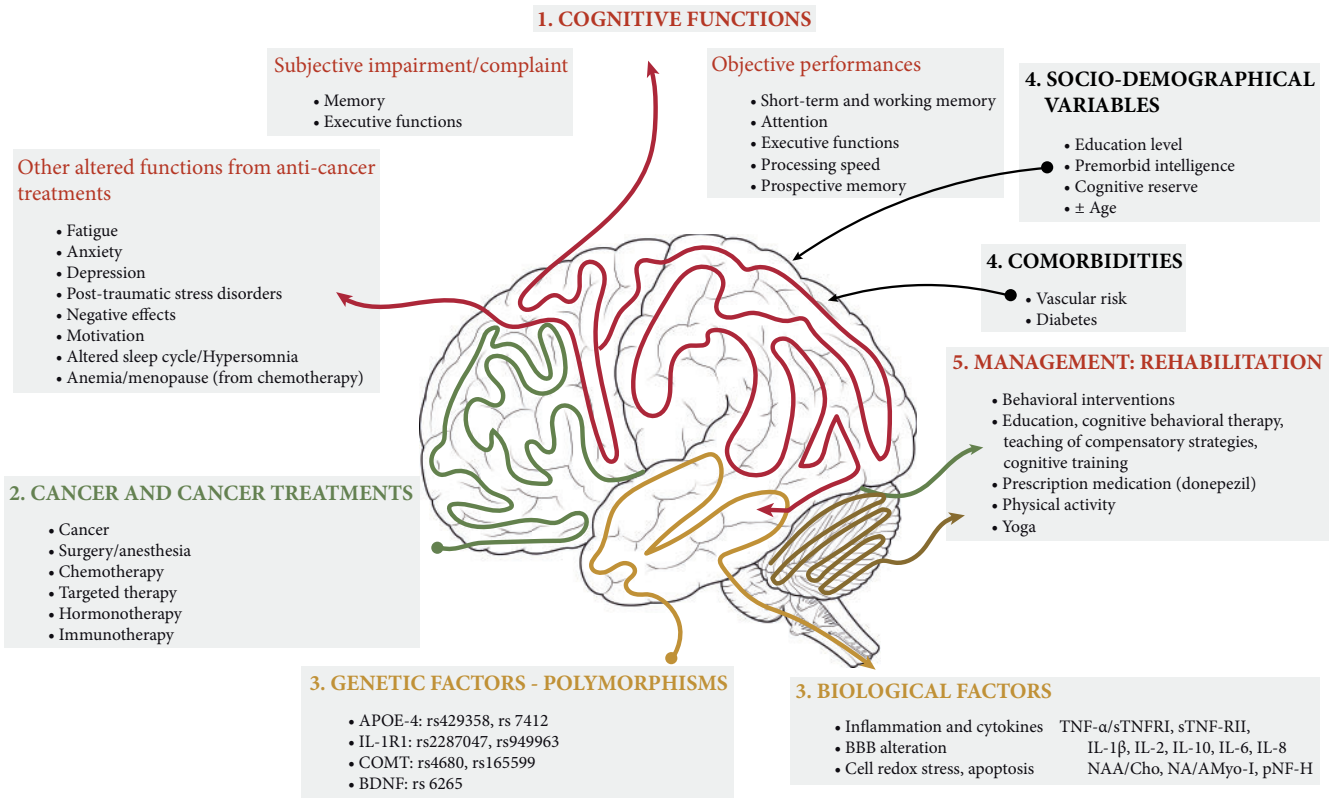

Figure 1. Schema outlining the complexity of cancer-related cognitive impairment. In cancer patients and survivors, the effect of chemotherapy on cognitive functions has been shown to impact different brain areas involved in attention, processing speed, memory, and executive functions. Recently, newly developed therapies involving targeted therapy, hormone therapy, and immunotherapy also appear to affect cognitive functions. The cancer treatments were associated with changes in brain volume, metabolic, or network modifications potentially related to direct neuronal toxicity and inflammation and genetic polymorphism combined with the aging process, patients' emotional status, co-morbidities, or lifestyle. Cancer patients can be affected in multiple aspects, highlighting the urgency of initiating specific onco-neuro-psychological patient care. APOE, Apolipoprotein E; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; Cho, choline; COMT, catechol-*O*-methyltransferase; IL1-R1, interleukin-1-receptor1; Myo-I, Myo-inositol; NAA, *N*-acetylaspartate; pNF-H, phosphorylated neurofilament subunit H; TNF-α, tumour necrosis factor-alpha; sTNF-RII, tumour necrosis factor-receptor type II.

Neurological markers or factors also detected during cancer treatments included decreased N-acetylaspartate (NAA)/choline (Cho) and NAA/myo-inositol (myo-I) ratios [85]. The breast cancer group with the lowest ratios reported reduced cognition, highlighting defects in the neurobiological status post-chemotherapy [85]. The serum axonal phosphorylated neurofilament subunit H pNF-H level in patients undergoing chemotherapy for breast cancer increased in a cumulative dose-dependent manner, suggesting its potential application as a biomarker of neural damage post-chemotherapy [86].

The potential role of genetic single nucleotide polymorphisms (SNPs) has been explored in other recent studies. Based on the inflammation-associated cognitive dysfunctions, a protective relationship between the SNP IL1R1 rs2287047 and cognitive complaints was established in breast cancer survivors. However, the SNP IL1R1 rs949963 was shown to be a significant genotypic predictor with breast cancer patients carrying the rare 'A' allele (e.g. GA + AA) having lower perceived attentional function [87], highlighting the complexity of cytokine SNPs. One of the first candidates suspected was the gene encoding *apolipoprotein E (APOE)*. The allelic variants *APOE-4* is a well-known risk factor for Alzheimer's disease. *APOE-4* may also contribute to poorer cognitive performance following chemotherapy and/or hormonal therapy in breast cancer patients [88]. Furthermore, an association between *APOE* status, breast cancer treatment, and cognition were found and moderated by smoking history [78]. Prefrontal volume reductions specific to patients treated with chemotherapy were associated with poorer cognitive performance related to an increase in TNF-α and in *APOE-4* carriers, providing a strong relationship between inflammation, brain functions and cognitive impairment post-chemotherapy [10].

The role of neurotransmitter metabolism as a potential genetic risk was reported with the catechol-*O*-methyltransferase (COMT) which catalyses the metabolic breakdown of catecholamine. Rs165599 in the *COMT* gene was correlated with impaired retrospective memory in patients receiving chemotherapy, suggesting that the COMT metabolic pathway is a determinant in CRCI [89]. Furthermore, the BDNF polymorphism (rs6265) [Val66Met] was implicated in the decreased

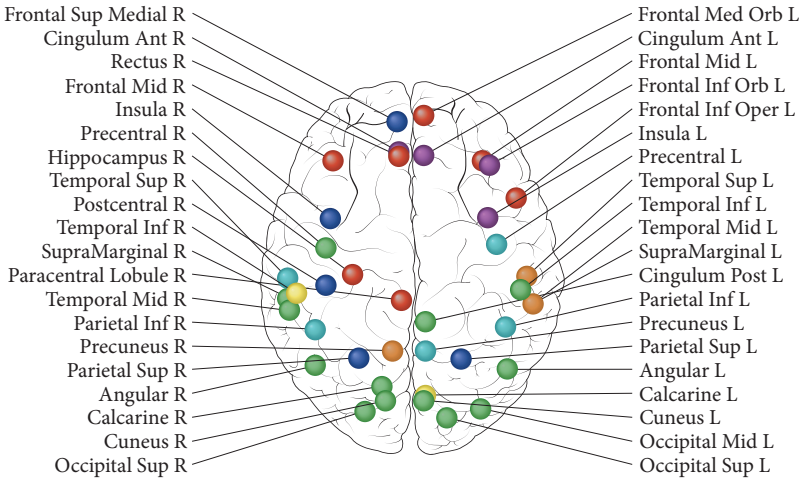

Figure 2. Brain regions that show changes in brain morphology, perfusion and/or activation after chemotherapy as reported by longitudinal studies issued from Li & Caeyenberghs, 2018 [11]. Changes in morphology [voxel-based morphometry (VBM) of grey matter or diffusion tensor imaging of white matter] are indicated in red. Changes in perfusion [arterial spin labelling (ASL)] are indicated in green. Changes in brain activation (fMRI) are indicated in blue. Several brain regions reveal overlap between modalities: magenta for overlap between brain morphology and activation, cyan for overlap between activation and perfusion, yellow for overlap between morphology and perfusion, orange for overlap between the three modalities. White matter regions are not included in the figure, nor was the cerebellum. However, two fMRI studies have revealed changes in the right cerebellum (lobule 4–5 and Crus- 2). The longitudinal studies are including cancer types, sample sizes, and chemotherapeutic agents: morphological changes—VBM: [10] 22 TC+, 43 TC−, 25 HC; bleomycin, etoposide, and cisplatin; [91] 8 BC+, 6 BC−; doxorubicin and cyclophosphamide/fluorouracil, epirubicin, cyclophosphamide, with or without docetaxel. In two patients, trastuzumab was also administered; [92] 14 GC+, 11 HC; capecitabine, oxaliplatin; [93] 19 BC+, 19 HC; fluorouracil, epirubicin, cyclophosphamide, docetaxel/cyclophosphamide, docetaxel/cyclophosphamide, doxorubicin; [94] 16 BC+, 12 BC−, 15 HC; doxorubicin/cyclophosphamide/paclitaxel, docetaxel/cyclophosphamide, docetaxel/carboplatin, docetaxel/doxorubicin/cyclophosphamide, docetaxel/cisplatin, paclitaxel. DTI: [95] 22 TC+, 43 TC−, 25 HC; bleomycin, etoposide, and cisplatin; [96] 34 BC+, 16 BC−, 19 HC; fluorouracil, epirubicin, and cyclophosphamide with or without paclitaxel; [97] 26 BC+, 23 BC−, 30 NC; doxorubicin, cyclophosphamide with or without docetaxel or paclitaxel, fluorouracil, epirubicin, cyclophophamide. Changes in perfusion: [98] 31 BC+, 34 HC; doxorubicin, cyclophosphamide, docetaxel; [99] 27 BC+, 26 BC−, 26 HC; doxorubicin, cyclophosphamide, paclitaxel/docetaxel, cyclophosphamide//docetaxel, doxorubicin, cyclophosphamide/docetaxel, cisplatin/doxorubicin, cyclophosphamide/paclitaxel. Changes in activation: [100] 18 BC+, 12 HC; doxorubicin, cyclophosphamide with or without docetaxel. One patient also received trastuzumab; [101] 18 BC+, 16 BC−, 18 HC; fluorouracil, epirubicin, cyclophophamide, with or without paclitaxel; [92] 14 GC+, 11 HC; capecitabine, oxaliplatin; [102] 21 BC+, 21 HC, fluororacil, epirubicin, cyclophosphamide, docetaxel/cyclophosphamide, docetaxel/cyclophosphamide, doxorubicin; [103] 16 BC+, 12 BC−, 15 HC; doxorubicin/cyclophosphamide/paclitaxel/docetaxel/doxorubicin, cyclophosphamide/doxorubicin/cyclophosphamide [20] 28 BC+, 24 BC−, 31 HC; doxorubicin, cyclophosphamide with or without docetaxel or paclitaxel/fluorouracil, epirubicin, cyclophophamide. BC, breast cancer; TC, testicular cancer; GC, gastric cancer; HC, healthy controls. Reprinted from [11], Copyright (2019), with permission from Elsevier.

susceptibility of cognitive complaints in breast cancer patients receiving some chemotherapy regimens [90].

Imaging of brain changes after cancer treatments

Many studies have reported reductions in grey matter volume or density, reductions in white matter microstructure, changes in brain activation and connectivity post-chemotherapy [3] (Figure 2) [11]. Findings of functional hyperactivation and hyperconnectivity of brain regions that support cognition have been interpreted as compensatory processes for treatment-induced brain injury [19, 20].

A decrease in white matter microstructure specific for chemotherapy-exposed patients 3–4 months post-treatment were observed in breast cancer patients, associated with performance decline in attention and verbal memory [96]. Three to four years of follow-up suggested cognitive and brain recovery [104].

A study evaluating breast cancer survivors 20 years post-chemotherapy showed worse performance on neuropsychological tests and global reductions in grey matter volume relative to a control group, comparable to 4 years of normal brain aging [105].

A prospective study evaluating early effects of BEP chemotherapy (bleomycin, etoposide, cisplatin) exposure on brain structure assessed testicular cancer patients after surgery but before further treatment and again 6 months later [10]. Widespread reductions in grey matter density occurred, with prefrontal reductions specific for the chemotherapy-treated patients (3 months post-completion) associated with cognitive decline. Network analyses carried out by DTI revealed altered global and local brain networks that were also associated with cognitive decline [106]. Ten years post-BEP chemotherapy, testicular cancer survivors had changes in white matter structure and cognitive decline compared with non-exposed survivors [107].

Some evidence indicates that the type and extent of neurotoxicity depend on the type of chemotherapy. In breast cancer survivors 2 years post-treatment, resting-state functional magnetic

resonance imaging showed anthracycline-based chemotherapy was associated with lower connectivity of the default mode network in addition to showing more cognitive impairments than patients treated with other cytotoxic regimens [108]. In breast cancer survivors 10 years post-treatment, multimodality MRI revealed treatment dose-dependent effects on grey matter volume, white matter microstructure and task activation [109, 110].

In addition to providing an assay for neurotoxicity, neuroimaging measures might provide a means to identify patients at high risk for treatment-induced cognitive decline, such as those with suboptimal brain network characteristics [63, 111].

Management strategies

A survey conducted in ~1600 survivors (>85% breast cancer survivors), at a median of ~3 years after cancer treatment, found 75% of participants self-reported cognitive symptoms related to cancer treatments [5]. Three quarters of respondents reported cognitive symptoms impacted their ability to return to work. Most participants (75%) wished to receive support, particularly cognitive training (72%). This highlights the importance of monitoring for CRCI. Strategies of management of CRCI have been studied [112–127].

Physical activity

A few studies have shown exercise programmes can improve cognitive complaints [118, 126] but most have not assessed objective cognitive function [116]. However, a recent study evaluates cognition in sedentary breast cancer survivors randomized to a 12-week exercise programme compared with a wait-list control group. The exercise group had improvement in processing speed in those diagnosed within the previous 2 years, and reduction in cognitive symptoms [126]. Another analysis of survivors randomized to eight sessions of yoga versus controls found improvement in cognitive symptoms in the yoga group [118]. In rat models, physical exercise has been shown to reduce cognitive deficits induced by chemotherapy by preventing diminished hippocampal neurogenesis [119].

Behavioural

Behavioural interventions generally focus on education, cognitive behaviour therapy and/or teaching of compensatory strategies, or cognitive training. Cognitive behaviour therapy and cognitive rehabilitation studies in cancer survivors consistently report improvement in cognitive complaints but show variable results for objective cognitive tests [117, 120].

The largest cognitive training study randomized cancer survivors ($n = 242$) with cognitive symptoms 6–60 months after adjuvant chemotherapy, to a web-based rehabilitation programme done at home, or a control group [112]. There was significant improvement in self-reported cognitive problems, anxiety/depression, and fatigue, but no significant differences among the groups on neuropsychological testing. Two smaller cognitive training studies in breast cancer survivors also found improvement in cognitive complaints but reported improvement in some aspects of objective cognitive function [121, 122].

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

Pharmacological

There is no evidence to support the use of pharmacological agents, such as erythropoietin or methylphenidate, in randomized controlled trials for the treatment of CRCI [1], as reported in a recent review [128]. At this time, clinical trials testing diverse neurostimulating, neuroprotectants or antineuroinflammatory therapeutic agents are currently in test phase, with the objective to prevent or treat CRCI. Efficacy of neurostimulants such as methylphenidate or modafinil is diverse and clinical experience concerning antidementia drugs (e.g. donepezil, memantine) is limited [128].

Work in animals suggests that several drugs, including fluoxetine [115], donepezil [38], and cotinine, the main derivative of nicotine [113], can improve cognitive performance as well as emotional state following chemotherapy, but further research is required.

Discussion

Conclusions and future directions

Cognitive impairments are reported during and after treatment in cancer patients receiving chemotherapy. Even if other treatments, such as hormone therapies in breast and prostate cancer patients, seem to have lower impact on cognition, the real current difficulty is to assign selective cognitive disorders to specific treatments because surgery, anaesthesia, and radiotherapy are often part of treatment. Further studies are needed to take into account the care trajectory and investigate the impact of newer therapies such as the new generation of hormone therapies in prostate cancer and immunotherapy, with preliminary data supporting cognitive alterations.

While there has been progress in identifying factors involved in CRCI (psychological and sociodemographic variables or biomarkers and genetic predisposition), complementary studies, including work with animal models and neuroimaging, are needed to define precisely which factors predispose to a higher risk of cognitive impairment.

Translational research, including clinical, imaging, and animal models has improved knowledge about CRCI. Studies on animal models have helped identify neurobiological mechanisms, highlighting a strong translational role for animal models in this field. Neuroimaging studies have provided valuable insights into functional and structural brain regions and networks affected by cancer treatment. As imaging methods continue to develop, we expect these will aid in uncovering the biological mechanisms involved and identifying patients at high risk for cognitive decline.

Significant progress in the field has been made utilizing traditional neuropsychological tests and validated self-report measures of cognition. However, concerns have been raised about the sensitivity and specificity of traditional neuropsychological tests to detect the relatively subtle cognitive changes often experienced

by cancer survivors. Some investigators are advocating the addition of tests based on cognitive neuroscience, which may be more sensitive and assess specific subcomponents of cognitive processes [129] with the use of more ecological tests.

There is limited high-quality evidence guiding how best to help cancer survivors with cognitive complaints. No pharmacological agents have been approved to reduce CRCI and, despite encouraging results with animals, none of the drugs examined in animal models have been subjected to clinical trials. For those with sustained impairment, or for whom impairment impacts daily function, referral to a neuropsychologist is recommended. Due to the association of cognitive symptoms with anxiety/depression, fatigue, and sleep disorders, it is essential to assess patients with CRCI for common symptom clusters and to treat these symptoms if present. The most promising strategy is likely cognitive rehabilitation but its impact on improvement in daily function remains unclear. Although only preliminary data are available, physical activity programmes could also be considered. More studies and especially robust clinical trials are needed to find adequate strategies of management of CRCI for routine oncology supportive care, to respond to demands and improve QoL of patients.

Multidisciplinary cooperation between oncologists, neurologists, imaging researchers, and neuroscientists is encouraged to define mechanisms of CRCI and to optimise medical care and patients' rehabilitation. Early detection of cognitive impairment is needed, especially in elderly patients who could be referred to an onco-geriatrician and/or neurologist to screen for cognitive impairment before and during treatment. Management of CRCI should be incorporated into clinical practice as for patients with neurodegenerative disease.

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