Chemotherapy-related changes in cognitive functioning

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1.   Introduction

The potentially detrimental effects of cancer and related treatments on cognitive functioning are emerging as a key focus of cancer survivorship research. Many patients with central nervous system (CNS) or non-CNS tumours develop cognitive problems during the course of their disease that can result in diminished functional independence and can continue well into the survivorship period.

In recent years, growing attention is being paid to the potential adverse effects of chemotherapy on brain and cognitive function. This central neurotoxicity may manifest as both acute and delayed complications. Virtually all categories of chemotherapeutic agent have been associated with adverse neurological effects, including both acute and chronic encephalopathy. More subtle cognitive dysfunction has also been demonstrated and frequently manifests as diminished memory, executive function, attention and information processing speed.

In this article on chemotherapy and cognitive functioning we will summarise knowledge on the incidence of cognitive deficits, the neuropsychological pattern and structural brain changes associated with chemotherapy, risk factors identified for developing neurotoxicity and underlying mechanisms as well as current treatment options to prevent or diminish the adverse effects of chemotherapy on cognition.

We will focus on chemotherapy-associated cognitive problems in breast cancer patients, as these symptoms have been particularly well studied in this patient group. In addition, studies on chemotherapy and cognition in adult CNS cancer patients will also be discussed. In this group of patients chemotherapy may be associated with stabilisation or improvement of cognitive function due to better disease control, but may at the same time go hand in hand with CNS toxicity as a consequence of chemotherapy.

2.   Neuropsychological studies in breast cancer patients

Over the last 10–15 years, increasing evidence has revealed the occurrence of acute and long-term cognitive problems for a subset of patients following chemotherapy applied in the treatment of non-CNS malignancies. In breast cancer patients alone, over 60 neuropsychological studies have been published that have investigated whether adjuvant chemotherapy is associated with cognitive impairment [1–3]. In the early years most of these studies had a cross-sectional design and provided us with a snapshot of the prevalence of cognitive impairment and the characteristics associated with this impairment at specific moments post-chemotherapy. In recent years, prospective neuropsychological studies on the incidence of cognitive problems arising from pre- to post-chemotherapy supported the previous observed relationship between chemotherapy exposure and cognitive problems by demonstrating cognitive decline post-treatment relative to pre-treatment cognitive performance.

Those prospective studies with a pre-treatment assessment also indicated the importance of a baseline measure, as several studies observed lower than expected cognitive performance in breast cancer patients who are about to undergo chemotherapy in comparison to reference data of non-cancer subjects or cancer patients with lower disease stages who will not need chemotherapy. Up till now, no explanation has been found for these decreased cognitive scores at baseline. Surgery (under general anaesthesia), distress, fatigue or disease-associated immune responses cannot yet clarify this observation.

3.   Frequency and pattern of cognitive dysfunction

The vast majority (70%) of the neuropsychological studies demonstrated cognitive impairment and/or cognitive decline

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in breast cancer patients who have been treated with cytotoxic agents compared to breast cancer patients without chemotherapy or compared to non-cancer controls, regardless of the design of the study.

Patients show deficits on a wide range of standardised neuropsychological tests, but core impairments are related to learning new information and accelerated forgetting of information. Impairment in executive functions – such as planning and implementing strategies, flexible shifting and working memory – is also common, as are deficits in psychomotor speed (indicative of a frontal–subcortical profile).

Despite the accumulation of knowledge on the cognitive side-effects of chemotherapy, the actual incidence of this impairment is still a subject of research. Estimates of affected patients vary from 17% to 78% across studies, because of differences between treatment regimens and between individual patients, but also owing to variations in study measures, assessment times and criteria applied to define cognitive impairment and deterioration. When the magnitude of the cognitive deficits as expressed in sizes of effects is studied, a large variation between studies is also observed.

4. Course over time

The literature has shown that cognitive changes can arise during treatment and can persist up to several years after completion of treatment. Studies have largely followed patients up to 1–2 years post-treatment. Only a few studies have investigated the very late (i.e. ⩾5 years post-treatment) effects of chemotherapy, but those that have show long-term cognitive problems in chemotherapy-exposed breast cancer survivors. A recent large study showed that breast cancer survivors who received CMF chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil) on average 20 years previously were more likely to have lower performance on memory, information processing speed and psychomotor speed compared with women without a history of cancer. The magnitude of the effects was comparable to approximately 6 years of age-related decline in cognitive function [4].

The influence of cancer and cancer treatment on the process of cognitive ageing is a topic that is increasingly receiving attention. There is concern that chemotherapy may induce accelerated ageing and that it can increase an individual's susceptibility to late-emerging cognitive decline or dementia. The underlying development of cognitive impairment in ageing appears to begin at mid-life. Genetic signatures of brain ageing (i.e. from transcriptional profiling in post-mortem brains) can be identified in subjects as early as their 40s. Substantial evidence demonstrates that a wide variety of variables in early life are determinants of cognition in later life. Furthermore, both lifestyle and health-related risk factors in mid-life are associated with poor cognition decades later. It is plausible that damage to brain health in young to middle-aged women becomes even more clinically evident many years later when the brain is extra vulnerable. Therefore it is essential to investigate how chemotherapy in earlier life may influence cognition in later life.

Different trajectories for chemotherapy-associated cognitive problems have been proposed in the literature. It could be that long-term cognitive problems result from lack of recovery from the acute effects of treatment. It could also be that the initial effect of treatment may produce a cascade of biological events that cause continued cognitive decline with ageing. Alternatively, chemotherapy may not be sufficient to cause enough redundancy loss to immediately affect cognitive function, but may produce a delayed effect as ageing continues, with the slope of change being influenced by a variety of factors [5].

Prospective studies with a very long-term follow-up or studies focusing on older cancer survivors are almost absent. A study on the effects of chemotherapy and cognition in patients ⩾65 years of age showed that these subjects experienced more cognitive decline than unexposed counterparts. Incidence of dementia was not explored in this study, and even though these subjects were of older age, their mean time since treatment was still relatively short [6,7]. A few retrospective studies have been published examining the risk of dementia in breast cancer survivors up to 15 years after completion of cytotoxic treatment; these studies used data from the linked Surveillance, Epidemiology and End Results (SEER)–Medicare database. None of these studies showed any clear evidence for the existence of such a relationship, although several methodological issues limit the validity and interpretation of the studies [8–11].

5. Risk factors

Several factors have been identified that generally increase the risk of developing neurotoxicity associated with chemotherapy. These include: (1) exposure to higher doses due to planned use of high-dose regimens, or to high concentrations of the parent drug and/or its metabolite due to impaired systemic clearance and/or pharmacogenetic modulation of drug pharmacokinetics; (2) additive or synergistic effects of multi-agent chemotherapy; (3) additive or synergistic effect of multimodality therapy that includes administration of chemotherapy either concurrently with or subsequently to cerebral radiation; (4) intra-arterial administration with blood–brain barrier disruption; and (5) intrathecal administration [12–17].

From the literature it is clear that not all patients are affected equally by chemotherapy. The finding that a subgroup of patients experience persistent post-treatment cognitive decline has led to the examination of patient- and disease-related risk factors for cognitive change. Candidate predictors of cognitive dysfunction frequently studied include age, education and pre-morbid IQ; however, no consistent predictors have been identified. Most studies failed to identify a relationship between treatment-related cognitive decline and age, IQ, education, baseline cognitive function and a host of other factors such as depression, anxiety, stress, fatigue, disease stage, haemoglobin levels and treatment-induced menopause. When an association between a sociodemographic or clinical predictor and cognitive dysfunction has been found the relationship is generally weak [3]. However, given the small sample sizes in nearly all studies, exploration of any sociodemographic or clinical predictors is likely to be underpowered. This is also the case for genetic factors (e.g.

vulnerable alleles of genes such as APOE and COMT) that have been examined as potential risk factors for cognitive decline [5].

Risk factors – endocrine treatment: a treatment-related risk factor for cognitive decline in breast cancer patients that is of particular clinical relevance is the combined use of endocrine therapy. Breast cancer patients undergoing chemotherapy often receive endocrine therapy as well. These therapies commonly consist of treatment with selective oestrogen receptor modulators (SERMs) such as tamoxifen and/or aromatase inhibitors (AIs) such as exemestane, anastrozole or letrozole. Evidence derived from basic as well as clinical research indicates that estradiol, within a time window of opportunity, can stimulate neuroplasticity in brain areas involved in cognitive behaviour leading to improved performance [18–20]. Since SERMs and AIs also target brain areas involved in the regulation of cognitive behaviour, it is plausible that these substances may contribute to cognitive deterioration in breast cancer patients. Blocking estradiol synthesis with AIs deprives the brain of modulation via estradiol and therefore theoretically results in decreased neuroplasticity and impaired cognitive functioning. However, surprisingly, studies in breast cancer patients seem generally to indicate that AIs less consistently adversely influence cognitive functioning compared with SERMs [21]. Studies specifically addressing the interaction between chemotherapy and endocrine therapy are sparse and the majority of studies have been too small to adequately investigate this interaction. Absence of oestrogen neuroprotective action in the brain – in the natural, surgical or chemotherapy-induced postmenopausal brain – makes the brain possibly extra vulnerable to neural damage by chemotherapy [22].

Particularly in older breast cancer patients, treatment with SERMs seems to have a potentially detrimental effect on cognitive functioning [23]. Basic research is rather conclusive on the neuroprotective properties of SERMs in the absence of circulating estradiol, but the effects of chronic SERM administration on cognitive behaviour are more ambiguous. Cleary more research is needed, particularly on the effects of SERMs on the brain and behaviour in relation to age and the length of deprivation of endogenous estradiol.

Risk factors – information: information on chemotherapy-associated cognitive problems is more and more accessible to patients. The reporting of cognitive problems may also be influenced by strictly cognitive mechanisms that are not rooted in psychological distress or negative affect, but simply in the extent to which a patient is informed about the possibility of cognitive problems following chemotherapy. Several studies on cognitive deficits in breast cancer patients showed that mere information about the association between chemotherapy and cognitive problems resulted in lower memory performance and higher complaint reporting [24,25]. These effects occurred independently of negative affect and pre-existing knowledge. The notion that mere information can add to the occurrence and maintenance of cognitive problems is derived from a large body of social psychological research on stereotype threat and priming. Stereotype threat – i.e. fear of confirming a stereotype – has been researched extensively, and evidence shows that activation of a stereotype or schema unconsciously leads to behaviour that is in correspondence with that stereotype [26,27].

Concepts of stereotype threat and priming are important for explaining the effects of treatment-related information on complaint reporting and neuropsychological test scores. Furthermore, it may be that some individuals are particularly vulnerable to these effects. Research shows that stereotype threat effects are stronger among people who are especially cognizant of the particular stigma, and that participants who self-identify more strongly with a stereotyped group show stronger stereotype threat effects on cognitive function [28]. A recent study showed that receipt of stereotypical information about the occurrence of medical problems experienced by cancer patients primed the cognitive accessibility of the cancer patient stereotype and differentially affected women's cognitive complaints and test scores, depending on their level of consciousness of cancer patient stigma [29].

It is not suggested that these psychological processes should be viewed as alternative explanations for biological influences. Rather, the possibility is raised that, for certain patients, self-regulatory and expectancy processes may also play a role – as a contributing, additive or meditational influence – in cognitive functioning. The next steps for clinical practice include the determination of the severity and duration of priming effects and to further understand the individual variation in these effects. In addition there is a need to explore the possibilities of diminishing or preventing these effects.

6. Neuropsychological studies in patients with central nervous system tumours

Evaluating adverse effects of chemotherapy on cognitive function in CNS cancer patients is often challenging because of the variety of other factors that can impact cognition in this population, most notably treatment with radiation and tumour progression. Both radiation and chemotherapy have been reported to share at least one common mechanism for their adverse effect on brain and cognition: disruption of the neural stem and precursor cell function [30]. Only recently clinical trials have incorporated cognitive testing into their study design, providing the opportunity to address these issues in large samples of homogeneously treated patients.

Radiation therapy has been demonstrated to adversely impact brain and cognition through vascular damage and inflammation, and via damage to neuronal progenitor cells affecting hippocampal neurogenesis and oligodendroglial formation [31]. Impairment in processing speed, attention, executive function and memory is commonly seen in brain tumour survivors previously treated with radiation therapy [32]. Several recent retrospective studies have examined the effects of radiation dose on different areas of the brain and cognitive outcomes. These studies provide evidence of a dose–response relationship between radiation to the bilateral hippocampal region and memory function [33], in addition to other brain regions and more heterogeneous cognitive outcomes [34]. Trials are currently under way in many centers to explore the use of technological advances in radiation

delivery to spare normal tissues from radiation exposure, and to explore different forms of radiation such as proton therapy that may similarly achieve reduced-dose exposure to the normal brain and other critical structures.

The standard of care for glioblastoma patients has included concomitant chemoradiation and adjuvant chemotherapy with temozolomide since 2004 [35]. A small single-institution study with standard-dose temozolomide reported cognitive decline in three out of 13 progression-free patients after concurrent chemoradiation and three cycles of adjuvant chemotherapy [36]. Declines were evident in psychomotor speed, attention and executive function, but not in verbal memory or working memory span. The results of a larger multi-institutional cooperative group trial comparing adjuvant standard-dose temozolomide and dose-dense temozolomide have also been reported [37]. In patients that were clinically and radiographically progression-free after concurrent chemoradiation and three cycles of adjuvant chemotherapy, 30% demonstrated cognitive decline, with no differences between arms. Cognitive decline was evident in all domains assessed – including verbal learning and memory, executive function and processing speed – and was prognostic of progression-free and overall survival. A recent study using temozolomide-administered rodents has demonstrated reduced hippocampal neurogenesis, decreased theta activity as measured by electromyography during an eye blink conditioning task and disrupted learning [38].

Due to the importance of angiogenesis in the growth and spread of cancer, there has been a great interest in inhibitors of vascular endothelial growth factor (VEGF), such as bevacizumab. Anti-VEGF agents have been demonstrated to produce rapid radiological improvement, ostensibly due to their ability to reduce tumour and blood–brain barrier permeability associated with leaky blood vessels. There is concern that this represents a 'pseudoresponse' which complicates the interpretation of traditional imaging end-points [39]. A phase II non-comparative study of bevacizumab in a recurrent glioblastoma multiforme (GBM) population included tests of cognition to characterise changes in brain function associated with bevacizumab therapy. In patients who achieved an objective radiographic response or who were clinically and radiographically progression-free at 24 weeks, the majority (75% and 70%, respectively) demonstrated stable or improved cognitive function relative to their pretreatment baseline [40]. Two placebo-controlled phase III trials with cognitive end-points in newly diagnosed GBM patients are currently under way and will provide more information on the impact of bevacizumab on cognitive function.

The long-term outcomes and associated reanalysis from the RTOG 9402 trial recently reported [41] a doubling of overall survival rates in pure or mixed anaplastic oligodendroglioma patients with 1p/19q co-deletion who received procarbazine, CCNU and vincristine (PCV) chemotherapy. This trial did not assess patient-oriented outcomes such as cognitive function to help determine the net clinical benefit of this survival advantage. However, two single-institution studies assessed cognition in anaplastic glioma [42] and GBM [43] patients treated with regimens that included PCV. Of patients with anaplastic glioma, 35% who were re-evaluated at a median of 8 months after initiation of treatment demonstrated cognitive decline. In GBM patients retested at a mean of approximately 8 months after initiating treatment, decreased cognitive function (in 44–52% of patients) was most commonly observed in the domains of psychomotor speed, executive function and memory. Unfortunately, these studies were not designed to distinguish the effects of chemoradiation from adjuvant chemotherapy and did not control for tumour progression, complicating the interpretation of these results as evidence of chemotherapy-related neurotoxicities.

Cognitive dysfunction is a frequent presenting/occurring sign in patients with primary CNS lymphoma (PCNSL). However, unlike patients with primary brain tumours, many PCNSL patients who receive chemotherapy with or without radiation therapy show evidence of improvement in cognitive function [44]. For example, Correa et al [45] reported improvements in executive function and verbal memory up to 2 years after treatment in newly diagnosed PCNSL patients who were treated with induction rituximab, methotrexate, procarbazine and vincristine followed by reduced-dose whole-brain radiation and consolidation high-dose cytarabine.

7. Neural substrate and underlying mechanisms

Despite evidence of cognitive changes associated with chemotherapy in cancer patients, the pathophysiology of these changes needs further elucidation.

Neuroimaging studies in breast cancer patients indicate structural changes in the brain associated with certain chemotherapeutic agents, and have started to shed light on the brain alterations that may be part of the mechanisms underlying the observed cognitive dysfunction in patients following administration of chemotherapeutic compounds without targeted CNS delivery.

8. Imaging studies

Several structural imaging studies have been conducted among breast cancer patients treated with adjuvant regimens, with assessments generally occurring from months to 3 years after completion of treatment [46–50], although two studies examined patients 10 and 20 years after completion of treatment [51,52]. Nearly all of these studies are indicative of structural brain differences between patients that received chemotherapy and either healthy controls or breast cancer controls that did not receive chemotherapy. White-matter pathology has been observed within months up to 10 years post-treatment, after both high-dose and standard-dose regimens. Studies using voxel-based morphometry have reported volume reductions in white and grey matter 1 year to 20 years after completion of chemotherapy. A prospective study observed focal grey matter volume decrease 1 month after the cessation of chemotherapy, which recovered in some but not all regions at 1 year post-treatment.

The cerebral white matter seems particularly vulnerable to the effects of chemotherapy. Studies investigating cerebral white matter integrity using diffusion tensor imaging (DTI) reported lower fractional anisotropy (FA) in the genu of the corpus callosum, lower FA in frontal and temporal white matter

and higher mean diffusivity in frontal white matter of breast cancer patients who received standard-dose anthracycline-based regimens compared with breast cancer controls and healthy controls. In a study conducted 10 years after completion of high-dose chemotherapy, DTI also showed lower FA in several white-matter tracts compared with breast cancer patients who never received chemotherapy [53]. In a large study conducted on average 20 years after completion of treatment, it was shown that in the absence of significant group differences in white matter integrity, time since treatment was inversely associated with lower global and focal white matter integrity within the breast cancer group [54]. This cross-sectional indication of affected white matter integrity was supported by a prospective study showing that breast cancer patients who received chemotherapy displayed significant decreases in FA in frontal, parietal and occipital white-matter tracts from pre- to post-chemotherapy, whereas for both a healthy control and a breast cancer control group, FA values were the same between baseline and follow-up [55].

Moreover there seems to be a link between the abnormal microstructural properties in white-matter regions and the cognitive impairments seen in breast cancer patients treated with chemotherapeutic agents; several studies observed correlations between abnormal diffusion properties and cognitive problems on neuropsychological testing [53].

The observed changes in DTI parameters may be related to demyelination of white matter axons or axonal injury after chemotherapy. Although caution is warranted in directly translating changes on structural imaging measures into biological changes, a rapidly increasing number of preclinical animal studies are helping define potential mechanisms underlying chemotherapy-induced cognitive dysfunction, and their results relate to a significant extent to the observations in human studies.

9. Animal studies

Valuable insights have come from preclinical studies on the potential pathogenic mechanisms involved in cognitive impairment related to systemic administration of chemotherapeutic compounds without targeted CNS delivery, although the precise mechanisms remain insufficiently understood. Many factors have been proposed to play a role in chemotherapy-induced neurotoxicity, including the directly toxic effects of chemotherapeutic agents on various brain cells, vascular injury and the indirect immune-mediated inflammatory processes. It is unlikely that a single mechanism can explain much of the major cognitive problems observed in cancer patients following chemotherapy.

Experimental studies have shown that many chemotherapeutic agents, when administered peripherally and in clinically relevant dosages, are associated with adverse effects on neurobiology and cognition (including 5-fluorouracil, methotrexate, doxorubicin, paclitaxel, cisplatin, BCNU and cyclophosphamide). In behavioural studies in animals, chemotherapy-related deficits have been observed in rodents on tasks that require involvement of the hippocampus and frontal systems. Toxicity is observed in multiple CNS cell types and multiple CNS regions [56]. Specifically, chemother-

apy-induced damage of mature post-mitotic oligodendrocytes and immature progenitor cell populations required for ongoing neurogenesis, gliogenesis and maintenance of white matter integrity seems to be an important aetiological factor in the development of neurotoxicity [57].

Research focusing on the development of strategies to inhibit specific transporters to enable drugs to cross the blood–brain barrier (BBB) in sufficient amounts is also relevant for understanding the mechanisms by which chemotherapeutic agents not targeted to reach the CNS cause cognitive and brain changes. Gong et al. [58] propose in their stem-cell hypothesis that differential sensitivities of glioma stem cells and neural stem cells to alkylating agents, temozolomide, cisplatin and targeted agents such as erlotinib and bortezomib hold the key to the resistance of primary brain tumours and the occurrence of chemotherapy-associated neurotoxicity in non-CNS disease.

The development of modalities that enhance delivery of drugs to brain tumours will also increase the drug exposure of the normal brain tissue, and may place patients at risk for treatment-induced cognitive decline. Until now, several preclinical studies have investigated pharmacological prevention strategies that further underscore the relevance of several hypothesised mechanistic pathways underlying the effects of chemotherapeutic agents on the brain and behaviour. Konat et al. [59] showed that N-acetyl cysteine, an antioxidant, ameliorated cognitive impairment in Wistar rats after combined administration of cyclophosphamide and doxorubicin. Two recent studies further explored potential candidates for interventions. A study by Lyons et al. [60] demonstrates that fluoxetine, when administered before and during treatment with 5-FU in rats, may prevent cognitive impairment and the loss of normal cell proliferation in the hippocampus observed after administration of 5-FU. Vijayanathan et al. [61] demonstrated that treatment with a glutamate receptor antagonist improved cognition after intrathecal administration of methotrexate in rats.

10. Interventions

Cognitive dysfunction is a common consequence for many cancer patients, and it does not always fade away. As indicated, pharmacological interventions to prevent or intervene against cognitive symptoms are in an early stage of development. Agents that have been examined or that are currently under investigation in patients include erythropoietin, methylphenidate, modafinil, donepezil and melatonin [62,63]. Some of these agents are promising, but the need for their rigorous testing with appropriate study designs and sufficient sample sizes precludes translation and implementation in daily practice.

Within the area of neuropsychological rehabilitation roughly two models can be distinguished: the restoration model and the compensation model [64]. The restoration model is directed at restoring damaged cognitive functions through function training, often using a so-called repeated practice approach, based on the assumption that specific stimulation induces plasticity. But evidence is still lacking that the benefits of training on specific tasks will transfer to

other untrained tasks or lead to any general improvement in the level of cognitive functioning. Compensation techniques, on the contrary, are proven to be successful. Improvement in daily life functioning can be achieved using intact cognitive abilities and strategies. Neuropsychological rehabilitation based on the compensation model together with psycho-education and coping strategies can be offered to cancer patients confronted with cognitive problems to maximise their ability to function [65].

11. Conclusion

Evidently, people with (a history of) cancer constitute an increasing group in our community. From this viewpoint, we have an obligation to obtain information on the cognitive effects of chemotherapy from a descriptive and preventive standpoint, and from an individual as well as a societal perspective. Chemotherapy is a necessary component in the management of many types of cancer, and the choices between different regimens in terms of adequate cancer control and minimal side-effects are restricted. Many cancer patients are returning to employment or other activities that may be affected by cognitive functioning. It is critical to identify cognitive effects of cancer treatment, to explore the mechanisms underlying these cognitive effects and to explore possible interventions that follow from these mechanisms and that may minimise cognitive side-effects and their severity and impact.

Conflict of interest statement

None declared.

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