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Monitoring and optimising cognitive function in cancer patients: Present knowledge and future directions

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ABSTRACT

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. We review the state of knowledge on the cognitive functioning of patients with primary and secondary brain tumours at diagnosis, during and after therapy, and discuss current initiatives to diminish cognitive decline in these patients. Similarly, attention is paid to the cognitive sequelae of cancer and cancer therapies in patients without CNS disease. Disease and treatment effects on cognition are discussed, as well as current insights into the neural substrates and the mechanisms underlying cognitive dysfunction in these patients. In addition, rehabilitation strategies for patients with non-CNS disease confronted with cognitive dysfunction are described. Special attention is given to knowledge gaps in the area of cancer and cognition, in CNS and non-CNS diseases. Finally, we point to the important role for cooperative groups to include cognitive endpoints in clinical trials in order to accelerate our understanding and treatment of cognitive dysfunction related to cancer and cancer therapies.

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1. Introduction

Compared to classical oncological outcome measures such as time to progression and survival, the importance of cognitive functioning in cancer patients has only recently been recognised. In patients with tumours either inside or outside the central nervous system (CNS), cognitive functioning is a critical outcome measure because cognitive dysfunction can have a large impact on the daily life of patients [1,2]. Even mild cognitive difficulties can have functional and psychiatric consequences – especially when persistent and left untreated. Deficits in specific cognitive domains such as memory, attention, executive function and processing speed may profoundly affect quality of life. For example, cognitive impairment negatively affects professional reintegration, interpersonal relationships and leisure activities. In addition, fear of future cognitive decline may also negatively affect quality of life.

Long-term cancer survivors are steadily increasing and many patients may develop cognitive dysfunction that can result in diminished functional independence. In this paper that focuses on cognitive functioning in cancer patients, we summarise the knowledge on the incidence and determinants of cognitive dysfunction in both patients with CNS and non-CNS cancers, the neuropsychological pattern and structural brain changes associated with various anti-cancer treatments, risk factors for developing neurotoxicity, as well as current treatment options to prevent or diminish adverse effects on cognition. Important knowledge gaps are discussed and future directions are presented. Specific attention is paid to the key role research cooperative groups hold to advance our understanding of cancer and cancer therapy-associated cognitive dysfunction – an understanding that forms the basis of preserving and enhancing cognitive function.

2. Cognition in primary and metastatic brain tumour patients

2.1. *Primary brain tumours*

The most commonly occurring primary brain tumours are gliomas (originating from the supportive cells of the CNS) and meningiomas (originating from the dural coverings of the brain), with annual incidence rates of approximately 7 and 9 per 100,000 per year respectively [3]. The incidence is low in absolute numbers when compared to the major cancer groups, but considerable when their impact on the health care system and the informal caregivers is concerned. Treatment usually consists of a combination of surgery, irradiation and chemotherapy, the choice depending on histological subtype and malignancy grade according to the World Health Organisation (WHO) classification [4,5]. The median survival ranges from approximately 14 months for glioblastoma (GBM, WHO grade IV) patients to more than 10 years for low-grade oligodendroglioma (WHO grade II) patients, and even longer for WHO grade I meningioma patients that have a 5-year survival of approximately 95% and are considered to be 'benign' tumours [5]. Patients with low-grade (WHO grade I and II) tumours typically present with epileptic seizures, whereas many patients with higher tumour grades (WHO grade III and IV) present with progressive neurological deficits [4].

2.2. *Metastatic brain tumours*

Approximately 20–40% of patients with a systemic malignancy will develop brain metastases during the course of their illness. Lung cancer, melanoma, renal cell carcinoma and breast cancer are the most common primary tumours that metastasise to the brain. Melanoma has the highest rate relative to other primary tumours, with 75% of patients with disseminated disease developing brain metastases. With best supportive care and depending on performance status, extent of extracranial disease, and age, the median survival time is approximately 1–2 months. Radiotherapy increases the median survival to 3–5 months, and further survival benefit might be achieved in specific subgroups through combinations of surgery, stereotactic radiotherapy, whole brain radiotherapy (WBRT) and systemic therapies [6]. The initial symptoms patients present with are similar to patients with primary brain tumours, but cognitive dysfunction, including memory problems and mood or personality changes, is already present in 90 percent of patients with brain metastases [7].

2.3. *Cognitive functioning at presentation*

Even at first presentation, many, if not all, patients with primary and metastatic brain tumours have cognitive deficits. Reijneveld et al. showed that patients with presumed low-grade glioma (WHO grade II) already suffered from cognitive deficits compared to matched healthy controls [8]. The same is true for patients with high-grade glioma prior to surgery [9] or prior to the initiation of radiotherapy [10]. Contrary to what was presumed historically, even most patients with suspected WHO grade I meningiomas show subtle cognitive deficits [11]. In patients with brain metastases [7], cognitive dysfunction is more correlated with the volume than with the number of metastases [12]. In general, cognitive deficits manifest in accordance with our traditional understanding of brain behaviour relationships – specifically, greater deficits in verbally mediated cognitive functions are seen in patients with left hemisphere tumours compared to patients with right hemisphere tumours. However, when compared to patients with stroke, more subtle and diffuse patterns of cognitive deficits are seen in patients with brain tumours [13].

2.4. *Cognitive functioning during treatment*

Virtually all patients with gliomas and metastatic brain tumours cannot be cured from their disease. Therefore, palliation of symptoms and sustained or improved quality of life are considered as equally important treatment goals as prolonged survival and postponed tumour progression. Evaluation of treatment outcome in brain tumour patients should therefore focus beyond survival endpoints, and should also aim at avoiding adverse treatment effects on the normal brain

to ensure optimal social and professional functioning. Research in this area during recent years has provided several important insights. As stated, numerous studies have demonstrated that the tumour itself can have a profound adverse impact on cognition. Resecting the tumour in a symptomatic patient may result in both deterioration and improvement of cognitive functioning.

Tumour progression during or after state of the art first-line treatment for GBM is frequently accompanied by rapid cognitive decline [15], and cognitive deterioration has predictive power regarding survival [14–16]. While most GBM patients with stable disease after first-line treatment show stable cognitive functioning, a substantial minority evidences signs of cognitive decline [14–18].

Seizures and treatment with older antiepileptic drugs (AEDs) in particular might have a negative impact on cognitive function of primary brain tumour patients [17], while newer AEDs might have no or even a beneficial impact on cognition [18,19].

The critical importance of assessing patient-oriented outcomes such as a cognitive function (arguably a cardinal symptom of a brain tumour) in brain tumour clinical trials is exemplified by the results of a recent large randomised trial examining the benefit of bevacizumab in patients with newly diagnosed GBM. In RTOG 0825 [20] as well as Avaglio [20,21], patients randomised to bevacizumab lived no longer than those randomised to placebo. Patients in the bevacizumab arm in both trials experienced a longer progression free survival. However, in RTOG 0825 patients with newly diagnosed GBM that received bevacizumab were found to demonstrate greater objectively tested and subjectively reported cognitive decline during the progression free period [20]. The evidence is mixed in terms of the impact bevacizumab has on patient's subjectively reported health related quality of life [20,21].

Several important observations were noted in a large trial of patients receiving WBRT for brain metastases with or without motexafin gadolinium, in which cognitive function was prospectively assessed at baseline and multiple intervals until death [7]. Over 90% of patients had evidence of cognitive impairment at baseline. The extent of impairment at baseline was correlated with lesion volume prior to treatment, and a higher baseline cognitive function was associated with a longer overall survival. In this trial, cognition, quality of life and functional independence were serially monitored at the same time points after therapy. Cognitive function was strongly associated with functional independence and QOL at baseline. Cognitive decline occurred sooner and was predictive of later reductions in QOL and activities of daily living [22].

2.5. *Long-term cognitive functioning*

With improved long-term survival for subgroups of primary brain tumour patients [23,24], the quality of that survival becomes even more essential. If treatments that result in effective tumour control are associated with cognitive impairments and worse health-related quality of life in the long run, longer survival may be less meaningful for patients. Klein et al. demonstrated that low-grade glioma patients with stable disease who had undergone radiotherapy had poorer cognitive function on an average 6 years following diagnosis and initial treatment compared to patients who had not undergone irradiation. Additionally, both groups had poorer cognitive performance than healthy controls and patients with haematological malignancies [25]. Patients who had undergone irradiation fractions >2 Gy were found to be at particular risk. Continued follow-up for another 6 years demonstrated that irradiated patients had further cognitive decline, while patients who had not undergone irradiation remained stable [26]. In another study, the impact of epilepsy and antiepileptic drug treatment on cognitive functioning and quality of life in these patients was examined. Eighty-six percent of patients had epilepsy and 50% of those using AEDs were actually seizure-free. The increase in epilepsy burden (based on seizure frequency and AED use) associated with significant reductions in all cognitive domains except for attention and memory functioning, was primarily attributed to the use of AEDs, whereas the decline in health-related Quality of Life (HRQOL) was ascribed to the lack of complete seizure control [17]. In a cohort of 27 progression-free anaplastic (WHO grade III) oligodendroglioma patients, status post irradiation with or without procarbazine, lomustine, vincristine (PCV) chemotherapy within the past twelve years, 30% were severely cognitively impaired [27]. These data suggest that glioma patients who respond favourably to first-line treatment might actually be at risk for long-term radiotherapy-related cognitive decline, although more information is needed to draw more definite conclusions. Moreover, no data exist regarding the long-term effects of chemotherapy on cognitive performance of brain tumour patients, stressing the need for long-term cognitive follow-up in brain tumour patients undergoing (experimental) first-line treatment [28].

2.6. *Prevention and rehabilitation*

Optimal safe treatment of the tumour is essential to aide in the preservation and possible restoration of cognitive functioning in brain tumour patients. Optimal treatment implies application of state-of-the-art resective surgical and RT techniques [26], avoiding excessively high fraction doses [29]. Damage to neural stem cells found in the subventricular zone and dentate gyrus in the hippocampus may play a role in preventing recovery from radiation induced memory deficits [29–31]. Gondi et al. [30] found that biologically equivalent doses of 7.3 Gy to 40% or more of the bilateral hippocampi corresponded with a 50% chance of developing memory decline within 18 months of completing radiation therapy. Intensity-modulated radiation therapy has been suggested as a way to spare neural stem cells when treating brain tumours [32]. Preliminary results from a recent phase II trial [33] found that administering whole brain radiation therapy with hippocampal avoidance when treating patients with brain metastases was associated with a substantial and statistically significant reduction in memory dysfunction four months after therapy. Previously, pharmacological intervention studies have not convincingly demonstrated effectiveness. The beneficial effects reported in some studies of psychostimulants [34] could at least in part be attributed to a placebo-effect, and the only proper placebo-controlled study did not

show an effect of modafinil over placebo with respect to symptom management [35]. Recently, a randomised placebo controlled trial of memantine reported delayed time to cognitive decline in patients with brain metastases that received whole brain radiation therapy [36]. Cognitive rehabilitation programs for the improvement of attention, memory and executive function, as well as comprehensive programs which combine neuropsychological and pharmacological treatment modalities may also be effective in patients with brain tumours [37].

2.7. *Knowledge gaps and future opportunities*

During the last decade, the neuro-oncological research community has become more aware of the importance of cognitive function as an outcome in experimental studies for primary brain tumour patients. Cognitive testing, utilising standardised tests with published normative data, moderate to high test–retest reliability, brief administration time and suitability for monitoring changes over time are becoming standard practice in most EORTC Brain Tumour Group clinical trials. Despite a growing understanding of the cognitive impact of CNS tumours and their treatment, we still have many knowledge gaps that need to be addressed in the coming generation of clinical trials, for which cognitive testing should be mandatory practice.

Small case series reports have identified differences in the cognitive sequelae from low- and high-grade brain tumours. However, we have a limited understanding of why these differences are present and how this may relate to therapies that maximise tumour control while minimising patient morbidities such as cognitive dysfunction. For example, do low-grade tumours exclusively offer an opportunity for the brain to reorganise, providing impetus for delayed or staged resections in patients at risk for surgically induced cognitive dysfunction? Are patients with IDH1-mutant tumours also good candidates for delayed or staged interventions? Can we identify who is at risk for surgically induced cognitive decline? Is it possible to predict who is most likely to experience functional re-organisation? Are there active approaches (i.e. cognitive training) that may facilitate reorganisation and/or restoration? Similarly, what patient factors (e.g. genetics, cognitive reserve) serve as protective factors that allow subsets of patients to tolerate therapies better than other patients? If we were able to identify comprehensive clinical–molecular phenotypes that predicted response and toxicity we would be better equipped to offer the most effective and safest therapy to our brain tumour patients.

While radiation therapy is a critical component of treatment for many brain tumour patients, and is delivered in relatively homogeneous doses at this time, it is unclear if the dose is optimal and safest for all patients. For example, some patients may be able to tolerate dose-escalated radiation without adverse effects, while others may receive equal tumour control and a better toxicity profile from a lower dose schedule. Different forms (e.g. photons versus protons) and delivery methods (e.g. intensity modulated, radiosurgery, whole brain with or without critical structure avoidance), as well as the use of radiosensitisers and neuroprotectants, have offered some promise in preventing or reducing cognitive decline associated with radiotherapy. However, we are only at the beginning stages of understanding and evaluating these issues.

Exciting results [23,24] have recently emerged demonstrating substantial gains in overall survival for patients with 1p/19q codeleted and IDH1 mutant anaplastic oligodendroglial tumours who received PVC chemotherapy and radiation [38,39].

However, routine formal cognitive testing was not performed in these studies. Cognitive assessment carried out with a small cohort of long-term survivors of the EORTC study showed that 30% were severely cognitively impaired [27]. The number of patients, however, was too small to determine the impact of the addition of PCV chemotherapy over RT alone on long-term cognitive functioning. The neuro-oncology community remains torn about the use of PCV as it is believed to be more toxic than temozolomide. Unfortunately, we have a very limited understanding of the cognitive effects of PCV and perhaps an equally limited understanding of the effects of temozolomide, which has been the standard of care chemotherapy for the largest group of primary brain tumour patients studied in clinical trials for almost the last decade. With the arrival of many new targeted agents and immunotherapies it is unclear if these will have greater or less cognitive effects.

Clearly there is a great need and opportunity to more fully understand the cognitive risks and benefits of these therapies that are being specifically directed at the brain, which may have ‘off target’ adverse effects on normal brain tissues, resulting in cognitive decline. Furthermore, we have relatively limited insight into the risk factors and time course of cognitive dysfunction in patients treated for CNS cancer, as not all patients develop this neurotoxicity and not everyone experiences these symptoms at the same time points. Linking cognitive outcomes with the correlative biological and imaging science within clinical trials will help enhance our understanding of the mechanisms accounting for cognitive decline and resilience, and inform future therapeutic trials designed to preserve or enhance cognitive function in this patient population.

3. Cognition in patients without central nervous system disease

In contrast to treatment for brain tumour patients, therapies for non-CNS disease are much more often given with the expectation of cure. Nowadays more than one in three people will be diagnosed with some form of cancer during their lifetime. For many people, treatments other than local therapies will be required for long-term survival, making the impact of such therapies on the patient’s well-being very important.

During the past years, a steadily accumulating body of evidence has indicated that a subgroup of cancer patients with non-central nervous system disease is vulnerable to treatment-related cognitive impairment. With respect to chemotherapy, human and preclinical studies into the occurrence and determinants of cognitive impairment in non-CNS cancer patients have demonstrated that many commonly used cytotoxic agents can drive neurobiological processes contributing

to cognitive impairment. Although cognitive dysfunction has been predominantly studied in breast cancer patients undergoing adjuvant chemotherapy, several clinical studies suggest that other cancer populations for whom chemotherapy is a treatment strategy (e.g. testicular and colon cancer) may experience similar cognitive symptoms. In addition, patients with haematologic malignancies might be particularly vulnerable to cognitive side effects, as treatments like CNS-prophylaxis, biological response modifiers and hematopoietic stem cell transplantation (HSCT) increase the neurotoxic burden. Cognitive effects of endocrine treatment for breast and prostate cancer may also occur, given the important role of hormones in the brain. While the research regarding hormonal therapies and cognitive functioning is inconsistent, recent reviews suggest potential negative impact on specific cognitive domains. Even with newer classes of compounds that target dysregulated cellular signalling pathways driving malignant cells, recent studies raise concerns about neurologic complications.

3.1. *Cognitive functioning at presentation and following chemotherapy*

The majority of prospective neuropsychological studies in breast cancer patients show that a substantial subgroup of patients have cognitive decline after chemotherapy, with incidence rates generally varying between 20% and 60% [40–44]. Patients show changes from pre- to post chemotherapy with regard to learning and memory, speed of information processing and executive functioning [45–48] (see for a detailed review Wefel [49]). A recent study in testicular cancer patients found that compared with a surveillance group, patients treated with mostly BEP chemotherapy had higher rates of cognitive decline at 12 months after treatment, with overall cognitive decline of 0%, 52% and 67% in the surveillance, low exposure and higher exposure chemotherapy groups respectively [50]. Similarly, a first prospective study in colon cancer patients receiving FOLFOX4 indicated adverse effects on verbal memory in a subgroup of patients [51]. In HSCT patients, objective cognitive decline has been found in nearly half of the patients at 1–3 months [52,53] and 16% of patients at 1 year post-HSCT [54]. Moreover, twice as many allogeneic HSCT patients compared to case-matched controls showed at least mild cognitive impairment at a 5-year follow-up [55]. In addition to the cognitive domains known to be affected in for example breast cancer patients, impairment in manual dexterity is common in HSCT recipients.

Cross-sectional studies of long-term breast cancer survivors indicate the presence of cognitive differences between chemotherapy-treated patients and non-cancer controls up to 20 years post-therapy, suggesting the persistence of cognitive impairment over the years [56,57]. Preclinical and childhood cancer survivor studies show that therapies including chemotherapy may accelerate aging [58], [59,60]. In what way cancer and cancer treatment in adult patients and patients of older age affect the trajectories of cognitive decline, is as yet undetermined but deserves intensified attention.

Intriguingly, studies that included baseline testing have found that cognitive impairment may already be present in various cancer populations before the start of treatment [61]. This phenomenon is putatively linked to inflammatory responses triggering neurotoxic cytokines, common risk factors for the development of cancer and cognitive decline, surgery-related factors or psychological distress/symptoms of fatigue and stressing the importance of pre-therapy assessment.

3.1.1. *Risk factors for cognitive decline*

In terms of disease-related and patient-related risk factors for cognitive decline, much research is still needed. There is some indication of a dose–response relationship. One study observed that more patients exhibited cognitive decline following high-dose chemotherapy compared to conventional dose chemotherapy [62], while another study showed a linear decline in cognitive performance after consecutive cycles of chemotherapy [63]. Nonetheless, direct comparisons of the toxicity profiles of common chemotherapeutic regimens are lacking. The finding that a subgroup of breast cancer patients experiencing persistent post-treatment cognitive decline has led to the examination of patient-related risk factors for cognitive change. However, until now, patient-related risk factors such as age, cognitive reserve, distress, presence of co-morbid conditions or other established risk factors, have not been identified as strong contributors to the impact of chemotherapy on cognitive function [44]. Given the small sample sizes in nearly all existing studies, exploration of sociodemographic or clinical predictors of cognitive decline is likely underpowered. This also holds true for genetic factors examined as potential risk factors for cognitive decline. The relationship between genetic polymorphisms, for example APOE and COMT, with cognition has not been consistent across the limited number of studies exploring this relationship [64]. Other studies on blood-based biomarkers that may mediate chemotherapy-associated cognitive decline suggest that the role of circulating proinflammatory cytokines in post-chemotherapy cognitive decline is still controversial and requires further evaluation [65].

3.1.2. *Neural substrates and underlying mechanisms*

In terms of neural substrates and underlying mechanisms, studies have documented white matter pathology in patients within a few months and after 10 years post-chemotherapy, for both high-dose and standard-dose regimens [66–69]. Studies using voxel-based morphometry have reported volume reductions of white and grey matter at one year [70] and 20 years after completion of chemotherapy [68]. Imaging studies indicate that chemotherapy seems to particularly affect the integrity [71] of the white matter with several studies demonstrating a link between the abnormal microstructural properties of specific white matter regions and cognitive impairments seen in patients treated with chemotherapeutic agents [72].

Advances at the basic science level are providing a detailed view of the pathogenesis of chemotherapy-related cognitive decline which may foster the development of better tools for early intervention and treatment. It is known that neural progenitor cells and mature post-mitotic oligodendrocytes are the most vulnerable cell populations to various chemotherapeutic agents [73,74]. Long-term cognitive decline in

cancer survivors may be the result of a combination of decreased proliferation of neural progenitor cells, impaired hippocampal neurogenesis and damage to oligodendroglial cells and white matter tracts [75]. As many different chemotherapeutic agents seem to have similar effects on the CNS, studies are also exploring common indirect mechanisms of neurotoxicity, such as pro-oxidative effects, toxic neurotransmitters/monoamine release, disruption of blood vessel density and supply and inflammation [76].

3.2. *Cognitive functioning and endocrine therapy*

A treatment-related risk factor for cognitive decline in breast cancer patients is the use of endocrine therapy with selective oestrogen receptor modulators (SERMs) and/or aromatase inhibitors (AIs). Evidence derived from basic and clinical research indicates that oestradiol administered within a specific window of time can stimulate neuroplasticity and improve cognitive performance [77–79]. SERMs and AIs also target brain areas involved in the regulation of cognition and behaviour and may contribute to cognitive changes. Blocking oestradiol synthesis with AIs deprives the brain from modulation via oestradiol theoretically resulting in decreased neuroplasticity and impaired cognitive functioning. Surprisingly, studies in breast cancer patients seem to generally indicate that AIs are less consistently adversely influencing cognitive functioning compared to SERMs [80,81]. SERMs bind to oestrogen receptors, but whether a given SERM will function as an ER agonist or antagonist is target tissue-dependent and varies among individual SERMs. Basic research is rather conclusive about the neuroprotective properties of SERMs in the absence of circulating oestradiol, but clinical studies demonstrate that treatment with SERMs has a detrimental effect on cognitive functioning, particularly in older breast cancer patients [82]. In view of the already widespread and potentially even more frequent long-term use of endocrine treatment in the future, more research is needed. Also, research addressing the interaction between chemotherapy and endocrine therapy is particularly sparse, and the majority of studies have been too small to adequately investigate this interaction. Absence of oestrogen neuroprotective action in the brain, either in the natural, surgical or chemotherapy-induced postmenopausal brain, potentially increases vulnerability to neural damage by chemotherapy.

Preclinical models used to assess the impact of androgen blockade on the brain have revealed adverse effects that are limited to specific areas, particularly the hippocampus, with deficits related to spatial abilities and encoding new memories [83,84]. A recent review of the influence of ADT on cognitive functioning of prostate cancer patients concluded that most studies do not provide substantial evidence of cognitive impairment with ADT. At the same time, the authors identified major methodological limitations of current research, including the omission of cognitive domains that are theoretically at the highest risk of being affected by ADT [85]. Based on the best controlled studies, a potential negative impact of ADT on spatial memory and verbal memory is suggested, and these studies stress the need for continued investigation of the impact of ADT on cognition. Given the large number of patients on ADT, cognitive side effects are important to consider, especially since more than half of new prostate cancers occur at an age where patients are already at increased risk for cognitive decline.

3.3. *Cognitive functioning and targeted agents*

The development of targeted agents focused on molecular or vascular pathways has transformed cancer treatment, improving efficacy. These innovative therapies are applied in the treatment of many cancers (i.e. sarcoma, colon, breast, renal and lung cancer) [86], usually for prolonged and repeated exposure, either alone or in association with traditional anti-cancer agents such as chemotherapy and endocrine therapy. Side-effects induced by these new treatments usually differ from those observed with chemotherapy, are class-specific, and some remain poorly documented. Their impact on inflammation and angiogenesis may specifically contribute to the onset of cognitive dysfunctions and/or increase of cognitive impairment induced by chemotherapy [87]. Based on their pharmacological properties, anti-angiogenic agents have been subjected to the most comprehensive investigation, indicating that patients treated with anti-angiogenic tyrosine kinase inhibitors report frequent severe fatigue and concentration difficulties, yielding a negative impact on quality of life [88]. Some clinical case series have been published reporting reversible cognitive disorders such as confusion, memory loss and word finding difficulties with the use of sunitinib. Additionally, rare but potentially severe posterior encephalopathy syndromes may occur with the monoclonal antibody bevacizumab, even in normotensive patients [89,90]. In a recent longitudinal study of renal cancer patients treated with anti-angiogenic tyrosine kinase inhibitors, a decline of objective cognitive functions from baseline was observed in 31% of cases (mainly executive functions and episodic memory), suggesting a direct neurotoxic effect of treatment [91]. However, the biological mechanisms implicated in these cognitive disorders remain unclear. Recent work suggests that vascular endothelial growth factor (VEGF) has a central role and that VEGF inhibitors might affect cognitive functioning through action on neurogenesis, cerebral blood flow and modulation of long-term potentiation [92,93]. Immune dysregulation and cytokine release are among the other postulated mechanisms [87].

The literature is limited regarding cognitive effects of other targeted agents. Some of those as mTOR inhibitors (rapamycin, everolimus) might actually provide protection from cognitive impairment. Indeed, preclinical work on everolimus has shown a potential for slowing the aging process [94] and decreasing the risk of Alzheimer disease. Proposed mechanisms of action include progressive desensitisation of normal brain insulin and IGF-1 responses, the aberrant proteostasis of Aβ and tau and the synaptic loss seen in Alzheimer disease. This collateral action might prove very useful for the growing elderly cancer population and is an area of research with potential to improve the tolerance of these new agents in the future [95].

Immunomodulators indicated in haematologic disease may also have potential negative impact on cognition when used in association with chemotherapy. Lenalidomide, a derivative of thalidomide with anti-tumour, anti-angiogenesis

and immunomodulatory actions, may induce particular cognitive disorders (notably episodic memory impairments) in some patients. The putative mechanism by which lenalidomide impacts cognition is not well known, though it is probably facilitated by specific risk factors, such as previous chemotherapy, prior mild cognitive impairment, age and the presence of cerebrovascular lesions. The anti-angiogenic effect might also prohibit neurogenesis in hippocampal structures and lenalidomide can cross the blood–brain barrier into the central nervous system, having a direct cerebral effect [96]. Since many other new agents in development target different specific pathways, assessing their potential impact on cognitive function will be a real challenge for the near future. These assessments will need to take into account symptom clusters including emotional factors, as mood alterations have been documented with agents such as the BKM120 oral pan PI3-kinase inhibitor [97] .

3.4. *The relation between cognitive symptoms and other cancer-related symptoms*

Cancer patients provide convincing testimony of distressing cognitive symptoms after cancer treatment, placing a burden on daily functioning. Cognitive dysfunction in itself alters mental functioning, causes distress, and results in reduced quality of life. However, cancer patients also suffer from the presence of multiple, often co-occurring symptoms, and isolated symptoms seldom reflect patients' clinical situation. These symptom clusters, if not attended to, could result in a less comprehensive approach to the management of cognitive problems. Understanding other symptoms in the context of cognitive dysfunction, such as fatigue, sleep disturbance, affective vulnerability and mood disorders might help determine how these symptoms contribute to the occurrence and persistence of cognitive impairment. Therefore, assessment of such symptoms should be an essential part of the clinical work-up.

Fatigue represents the most common side effect of cancer treatment and can persist in a substantial proportion of survivors, affecting physical, psychological and social well-being. Fatigue is strongly linked with sleep disorders and menopausal symptoms such as hot flashes [98]. These clustered symptoms have a severe impact on health-related quality of life. A recent comprehensive study of patients with different types of cancer, all receiving chemotherapy, revealed a high prevalence of insomnia symptoms and related syndromes. In a longitudinal study where almost 40% of patients experienced persistence of an insomnia syndrome, there was a connection with menopausal symptoms and fatigue, acting as triggers for the development of insomnia [99,100].

Cognitive dysfunction affects several aspects of quality of life, such as employment, social functioning and independence [101]. Although subjective cognitive complaints are at best weakly associated with tested cognitive function, self-perceived cognitive problems correlate much more frequently and stronger with fatigue, anxiety and depression [44,102]. The latter symptoms should be taken into account as they can affect perception of cognitive performance via attentional bias in which anxious and depressed people perceive their failures as more severe. Co-occurring anxiety and depression may also have synergistic effects on executive dysfunction, as shown by studies in which individuals with co-morbid depressive and anxiety disorders performed worse on some executive function tasks compared to individuals with depression or anxiety alone [103]. These findings stress the importance of systematic assessment of areas other than cognition. Specifically, early detection and intervention for mood, fatigue and sleep disturbances hold the possibility of contributing to the reduction of cognitive problems.

3.5. *Rehabilitation*

Unraveling the precise mechanisms underlying treatment-related cognitive side effects is necessary to enable the identification of novel treatment strategies. Pharmacological interventions to prevent or intervene against cognitive symptoms in non-CNS cancer patients are in the early stage of development. Some agents are promising, but rigorous testing with appropriate study designs and sufficient sample sizes necessary to translate and implement these agents in daily practice are either absent or have generated disappointing results [104]. For example several studies found positive effects of Erythropoietin (EPO) on cognitive functioning during or shortly after chemotherapy, but randomised controlled studies at longer follow-up failed to show positive effects of EPO on cognition. Psychostimulants like methylphenidate and modafinil have been tested in several studies, but the effectiveness of methylphenidate to treat cancer therapy associated cognitive dysfunction is at present not established. Initial small studies with modafinil are slightly more hopeful, but larger studies with longer follow-up are needed before conclusions about the effectiveness can be drawn [105]. Another example of an agent that received attention following initial interesting preclinical findings but for which convincing data from phase III studies on the efficacy is lacking, is donepezil. Multiple behavioural based studies have proven successful in improving daily life functioning using intact cognitive abilities and strategies together with psycho-education [106–111]. Interventions like mindfulness-based stress reduction and exercise interventions are gaining increasing attention as potential effective interventions for cancer and cancer-treatment related cognitive effects, and several large trials are underway which should clarify the value of these behavioural interventions. Likewise, interventions focusing on mental stimulation, collectively known as brain training, are frequently accessed by cancer survivors. Although reviews of the current brain training literature indicate that most programs still fail to display fundamental transfer, there is hope that the next generation of brain training programs capitalising on novelty to stimulate plasticity to the highest extent, will result in robust generalisation of trained skills [112].

3.6. *Knowledge gaps and future opportunities*

We have learnt that treatment-related cognitive decline occur in patients with non-CNS disease. This holds true for patients receiving chemotherapeutic agents, endocrine agents and

molecularly targeted agents. We have also learnt that cancer alone may be associated with lower than expected cognitive function, an as yet poorly understood finding that at the very least indicate the importance of a pre-treatment baseline measure. Most research has been done in the area of chemotherapy-related cognitive decline, but despite clear progress, several fundamental questions still need to be answered. These questions centre on the actual incidence of cognitive decline (e.g. how many patients are affected, and for which proportion of patients does cognitive decline interfere with daily life activities?) and on the trajectory of cognitive decline (i.e. does chemotherapy cause acceleration of aging or even put patients at increased risk for dementia?). And, are there regimen-specific toxicity profiles, and do these profiles change or increase in severity when combined with other treatment strategies, such as endocrine or targeted therapies? The considerable variation across patients in the presence of cognitive decline points to specific host factors that may drive the association between chemotherapy and cognitive decline. From the literature, relevant clues for these patient-related risk factors emerge, but these factors are unsatisfactorily clarified. Are patients of higher age and with lower cognitive or brain reserve more vulnerable, what is the influence of comorbid conditions, and can we identify genetic influences that modulate the exposure to cancer and cancer therapies?

The emphasis in the current literature has been on studying the effects of adjuvant chemotherapy for breast cancer, mainly assessing patients in their midlife. From the preceding review it is apparent that there is fair body of evidence linking a much wider spectrum of chemotherapeutic regimens for a variety of cancers to cognitive decline. In these patient groups, cognitive functioning should be monitored as well to understand which therapies are most and least likely to lead to cognitive decline. Regarding the role of endocrine therapies on cognitive functioning, much less research has been done, and a very complex body of findings has been reported. Many studies lack an adequate sample size and use non-optimal selection of neuropsychological tests (i.e. they do not assess domains expected to be impacted by changes in the hormonal milieu). From the current literature no reliable conclusion can be drawn on the presence, pattern and strength of cognitive effects of various endocrine therapies for patients with hormone-sensitive tumours, nor if the brain recovers from adverse effects after switching to a different class of agents or upon completion of endocrine treatment. Endocrine therapies are applied to many cancer patients, with a trend for even longer periods of administration. There is a high need to embark on endocrine therapy trials to gain adequate data regarding the cognitive effects of these therapies and to guide optimal treatment choices and best duration of treatment.

Finally, little is known about the cell–biological consequences of many new agents that target different specific signalling pathways. Assessing their independent impact on cognitive function as well as their influence when combined with other cancer treatments will be an important task in the near future, since there is evidence that similar signalling mechanisms are also implicated in the biology of neural progenitor cells and maintenance of brain plasticity.

4. Assessment of cognitive function: trial design opportunities

The importance of assessing cognitive functioning in brain tumour patients has been recognised and cognitive endpoints are added more frequently by cooperative groups including the EORTC Brain Tumour Group. The recent trend towards incorporating cognitive testing into clinical trials also in the case of patients with non-CNS disease is applauded and welcomed. The Response Assessment in Neuro-Oncology (RANO) working groups [113,114] and the International Cognition and Cancer Task Force (ICCTF) [49] have proposed a core set of cognitive tests measuring memory, executive function and processing speed and these tests are widely adopted by the EORTC, Radiation Therapy Oncology Group (RTOG) and other consortia. The tests can be administrated after a short training and do not need on-site neuropsychological expertise. The incorporation of such a brief cognitive battery into the main protocols enables accurate, efficient and unobtrusive monitoring of different therapies with respect to their potential cognitive sequelae and determine their relationships with other symptoms, with sufficient power to permit important subgroup analyses driven by biological hypotheses.

The inclusion of cognitive endpoints brings both opportunities and challenges, including developing a methodology for combining or evaluating the cognitive endpoints with the more traditional survival endpoints. Additionally, it should be clarified which clinical trials, in what phase, with which patient population, require or would benefit from inclusion of cognitive testing. For example, it could be argued that in trials of agents intending to reach the brain, monitoring cognition should be mandatory at any phase and in any patient population. Information from phase I and II trials would inform the development of phase III trials. Alternatively, one may argue that promising compounds should first pass the early safety screening phase, and then in the context of comparative effectiveness designs (as we have limited historical cognitive data for most agents) should routinely include cognitive testing. For many neurologic diseases cognition is the primary outcome. However, in oncology this has rarely been the case. Are there times when cognitive function is the best as a primary, secondary or exploratory outcome?

Running parallel to these issues are opportunities to further enhance the precision of our cognitive tests. Within the context of international trials, further improvements can be achieved by simultaneously collecting healthy control data, developing mechanisms to minimise missing data that confounded some prior trials, and by defining the frequency and timing of cognitive testing on study (e.g. should testing occur at fix intervals, every time the patient is restaged, should testing only be conducted when patients are stable or up until death?). We can also evaluate which statistical models are best suited to what study questions regarding cognition in these populations, standardise and validate a definition of clinical significance apart from statistical significance, and recognise and manage potential floor and ceiling effects in these outcome measures. Regardless of how these questions may be answered eventually, neurocognitive testing is a cornerstone of adequate care for CNS and non-CNS patients

facing cognitive decline. Moreover, the development of modifying interventions for cancer and cancer therapy-related cognitive decline will likely depend on the wide application of these cognitive diagnostic methods.

Research cooperative groups are best positioned to progress our knowledge on the cognitive effects of cancer and cancer therapies and present an excellent and cost-efficient utilisation of scientific assets to examine and promote cognitive health [115]. By routinely including cognitive endpoints in combination with other patient-oriented endpoints in clinical cancer trials, we can closely monitor and ultimately reduce the total burden of physical and mental morbidity. The EORTC survivorship initiative takes an important first step by recognising the need to include such patient-oriented endpoints in addition to standard efficacy endpoints in a more systematic way in order to provide better care for our cancer patients and the growing community of cancer survivors.

Conflict of interest statement

None declared.

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