An Oncologist's Dilemma: How to Effectively Eliminate CNS Cancers in Children with Radiation Therapy Whilst Preserving Cognitive Function?

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Abstract

Cranial irradiation is commonly adopted in the treatment of central nervous system (CNS) tumours, even in younger cancer patients, despite its severe early and late side effects. One of the major consequences of using radiation therapy in the CNS is the inevitable occurrence of normal tissue toxicity and resultant morbidities including cognitive dysfunction, learning impairments and a lower quality of life. These symptoms are in part due to an arrest in the production or survival of neural precursor cells in particular proliferative regions of the brain including the hippocampus. As the population of childhood survivors of CNS or metastatic malignancy grows, more attention must be paid to the debilitating cognitive co-morbidities resulting from radiation therapy in particular. Protective prophylactic pharmacological agents and precise 'hippocampal-sparing' radiation techniques should be considered during treatment, while drug or behavioral interventions may be indicated during a patient's long term follow up period. This brief review overviews radiation therapy uses and mechanisms, investigates some of the currently known cellular and molecular events that lead to functional decline post-irradiation, examines the scarce therapies available to childhood CNS cancer survivors for their long-term cognitive morbidities to date and identifies possible therapeutic niches that could be targeted either during or post-radiation therapy to attenuate its long term consequences in the human brain.

Introduction

Tumours of the central nervous system (CNS) represent the most common solid neoplasms of childhood and overall are one of the more prevalent childhood malignancies (38 cases per million per year in Ireland) (NCRI, 2014) and are second only to the paediatric leukaemias (Pollack and Jakacki, 2011). Survival rates for childhood cancer in developed countries have improved considerably over the last few decades (5-year survival rate of ~70% amongst childhood CNS cancer patients in Ireland (NCRI, 2014)), owing to highly specific diagnostic procedures and the implementation and improvement of multi-modal treatment strategies (Kaatsch, 2010). It follows that a growing number of people are living with the effects of their anti-cancer treatment and thus survivorship is an extremely important topic, but one that may have been overlooked in the past (Jena and Coles, 2015). Unfortunately, CNS cancer survivors tend to be at an increased risk for developing chronic health conditions with the severity of these conditions often depending on the mode of treatment adopted to cure their cancers (Oeffinger et al., 2006). Radiotherapy (RT) alone or in combination with surgery and/or chemotherapy is a common therapeutic strategy for children with CNS tumours treated in Ireland (NCRI, 2014) and elsewhere (Pollack and Jakacki, 2011). Cranial radiotherapy, despite often acting as a curative agent in CNS cancer, has been associated with the development of late neurocognitive sequelae – namely cognitive dysfunction - often characterized by impaired short term memory formation - in both adults (Dias et al., 2014) and children (Dietrich et al., 2008; Ellenberg et al., 2009; Mulhern et al., 2004). Often untreated, these deficits severely detract from the quality of life of childhood cancer survivors and have been correlated with lower academic and socioeconomic achievement (Ellenberg et al., 2009). In fact it has been estimated that of all patients receiving cranial RT at an age less than 7 years, nearly 100% require special education. After 7 years of age ~50% require special education while some degree of memory dysfunction is thought to occur in the majority of children treated in this manner (Monje, 2008).

Local changes in neurogenesis have been characterized in the adult and child response to ionizing radiation (Raber et al., 2004). It is believed that cranial irradiation's off-target effects include the reduction in the neural precursor cell (NPC) pool of the memory formation and consolidation areas of the brain - i.e. in the hippocampus (Dietrich et al., 2008; Madsen et al., 2003; Monje et al., 2002; Monje et al., 2007). Damage manifests in the form of neural precursor apoptosis, glial cell perturbations and micro-vascular disturbance (Belkaet al., 2001) and these effects are thought to underlie the problems associated with cognition in the childhood cancer survivor population.

Few therapies are available to alleviate late neurocognitive effects post-RT and few prophylactic or mitigating strategies exist to preserve neurocognitive function before RT takes place. Thus, it appears that new treatments are urgently needed for this growing patient population. Both preventative and alleviating therapies should be designed with NPC molecular and cellular mechanisms in mind.

Meanwhile the clinician is faced with the dilemma of whether or not to apply increased doses of radiation therapy to the childhood brain for curative or relapse preventative reasons - all the while, not knowing how severe neurocognitive sequelae will be in each patient and how they will treat them post RT. In some cases higher doses of RT may be associated with both better cure rates and greater morbidity. In contrast, protocols aiming to minimize toxicity may increase the risk of relapse, disease progression, metastasis, or death (Askins and Moore, 2008).

Below RT is discussed in terms of its indication, mechanism of action and its most serious late side effects in childhood CNS cancer patients. Survivors' long-term cognitive morbidities are identified and explained biologically followed by a brief review of current treatments and possible therapeutic niches that could be targeted to attenuate the long-term consequences of brain irradiation and arm clinicians with a greater battery of tools to manage their patients effectively.

RT Indications, Mechanisms and Side Effects

Radiation therapy (RT) is an effective treatment for CNS neoplasms. The benefit of cranial irradiation in a clinical setting largely resides in its ability to effectively target microscopic and/or gross intracranial pathologies (Gondi et al., 2010). The main goal when treating malignancies with radiation therapy is to deprive tumor cells of their reproductive potential. Ionizing radiation causes direct and indirect DNA damage that ultimately facilitates death or quiescence of tumour cells by apoptosis, mitotic catastrophe or cellular senescence. Rapidly proliferating cells tend to be particularly sensitive to the effects of irradiation, which allows RT to non-specifically and successfully eliminate tumour cells (Eriksson and Stigbrand, 2010). However, damage to normal, surrounding tissue constitutes a major problem, and radiation therapy is associated with early and late adverse side effects, particularly in pediatric patients. CNS malignancies carry the greatest long-term side-effects of any tumor site (Heath et al., 2012).

One major late side effect of cranial RT, that may manifest months to years after treatment, is neurocognitive decline. Children tend to show a greater degree of debilitating injury and neurocognitive deficits post-RT than adults. This is not surprising given the inherent vulnerability of the developing brain, its higher content of rapidly proliferating neural precursor cells (NPCs) (Fukuda et al., 2005) and its ongoing high levels of neurogenesis and synaptogenesis (Dietrich et al., 2008; Gibson and Monje, 2012; Monje et al., 2002). The intensity of neurocognitive symptoms seems to be negatively correlated with the age of the patient at the time of treatment and positively correlated with increasing dosage of RT delivered (Lawrence et al., 2010). The functional neurocognitive domains that are affected the most by cancer treatments are attention, executive functioning, processing speed, working memory, and ability to learn, which in turn adversely affect the academic performance of pediatric cancer patients and childhood cancer survivors (Askins and Moore, 2008; Mulhern et al., 2004). Given the significant burden of post-RT morbidities, one might question the need to use radiotherapy at all. However the usefulness of radiotherapy should not be overlooked as it is one of the most effective non-surgical treatments of primary brain tumors and metastases.

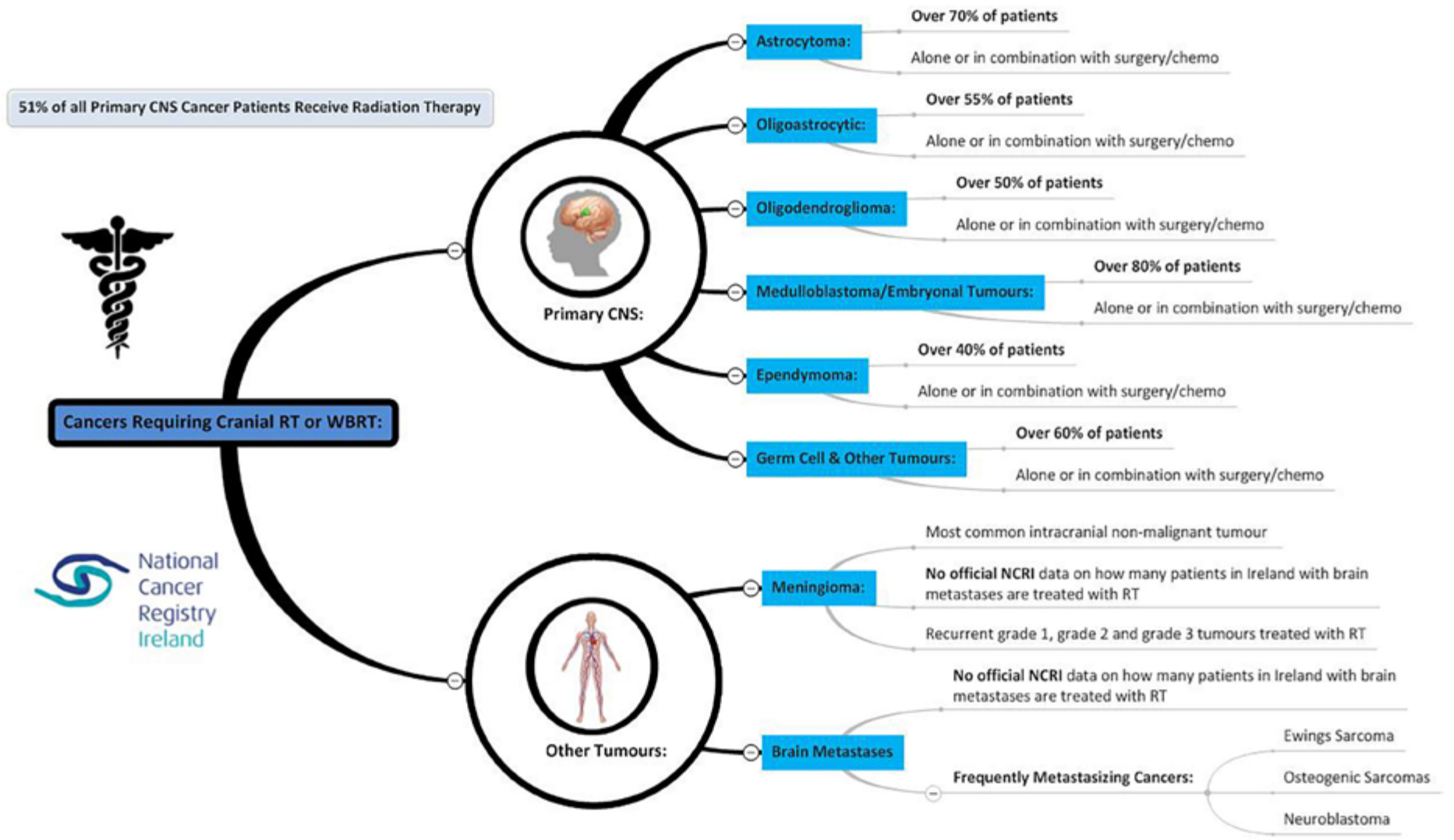

Figure 1. Schematic of CNS cancers requiring cranial irradiation (% of patients per year in Ireland).

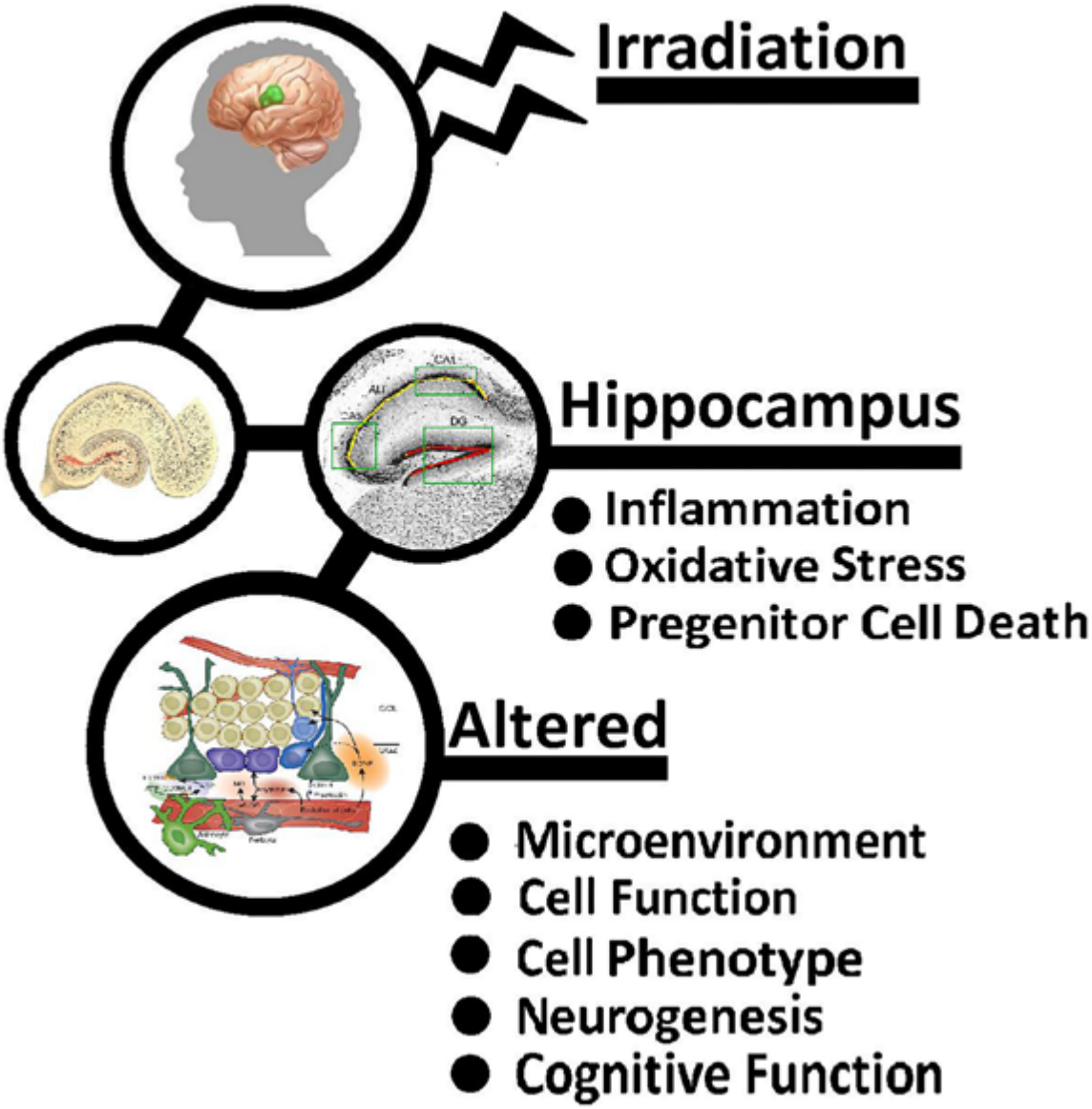

Figure 2. Schematic of radiation induced damage.

Cellular & Molecular Reasons for Neurocognitive Decline in Children

It was once thought that the neurocognitive decline that occurred in children post-RT was caused by direct damage to neuronal circuits. More recently, it was discovered that loss of cerebral white matter and near-complete ablation of the NPCs in proliferative regions of the brain are in fact causing at least some of the negative symptomology. White matter destruction is thought to partly account for changes in IQ score (Mulhern et al., 2004) while loss of NPCs in the hippocampus is thought to account for impaired memory formation in the irradiated infant brain (Gibson and Monje, 2012).

The latter observation has gained much attention in recent years and has become the subject of intense research due to its potential as a target for modulation. Much data has been gathered from rodent experiments (Kalm et al., 2013; Monje et al., 2002) and human studies (Monje et al., 2007). The formation of new memories has been associated with the lifelong mitotically active compartments of neural stem cells located in the sub-granular zone (SGZ) of the hippocampal dentate gyrus (DG)

Table 1. Current post-RT and pre-RT/preventative pharmacological strategies being studied worldwide	
Post-RT Interventions	**Preclinical/Clinical Stage? Effective?**
Donezapil	Studied in adults undergoing brain RT. Shows some improvement in cognitive function and mood (Shaw et al., 2006)
Methylphenidate	Prescribed to childhood cancer survivors with learning difficulties and shows some improved cognitive function (Meyers et al., 1998)
PPAR Agonists	Prevents cognitive impairment in irradiated rat model (Zhao et al., 2007)
Renin-Angiotensin System Blockers	ACE Inhibitors are being investigated in irradiated rat models. Data show reduced cognitive function change (Lee et al., 2012)
Pre-RT Preventative Strategies	**Preclinical/Clinical Stage? Effective?**
Memantine	NMDA antagonist used to prevent neuronal excitotoxicity. Reduces neuronal injury in rat models. Being investigated in a Phase III trial for adult whole brain RT and shows increased time to cognitive decline (Brown et al., 2013)
Indomethacin	Modulates inflammatory radiation response in rat model of neuroinflammation (Monje et al., 2003)
Lithium	Protects neuronal precursors in irradiated mouse model (Zanni et al., 2015)
Armodafinil	CNS stimulant that has been studied in adults receiving partial brain RT. Shown to reduce fatigue (Page et al., 2015)

and the subventricular zone (SVZ) in the lateral walls of the lateral ventricles (Eriksson et al., 1998). It has been shown in animal models that radiation induces apoptosis and loss of cells in the immature and juvenile rodent brain (Monje et al., 2002) and that the SVZ and SGZ are particularly susceptible to radiation-induced apoptosis. Decreases in cell proliferation and decreases in neuronal differentiation also occur in proliferative regions (Monje et al., 2002).

Recent studies have suggested that radiation not only directly induces cell death, but also affect the fate of the precursor cell pool by altering the local microenvironment. Radiation-induced inflammation was demonstrated to cause neural progenitors of the SGZ to differentiate into glial cells instead of neurons (Ekdahl et al, 2003; Monje et al., 2003). Hence, in addition to killing neuronal progenitors, radiation may direct the differentiation of remaining NPCs away from a neuronal lineage, resulting in further loss of neurons. Other micro-environmental determinants of neurogenesis include the presence of the trophic signals required for NPC proliferation, differentiation, survival, and the absence of inhibitory factors (Eriksson et al., 1998). In addition NPCs form a close anatomical relationship with the microvasculature in the neurogenic regions and this neurovascular relationship is believed to be crucial for nutritional and trophic support of newly formed neurons. Experimental models of irradiation injury often show that this niche also becomes perturbed post-therapy (Monje, 2008). In fact it has been noted that neurovascular damage sustained during the delivery of cranial RT in children may predispose these patients to further cerebrovascular issues such as stroke later in life (Roddy and Mueller, 2015).

An important negative regulator of the neurogenic microenvironment is microglial inflammation, particularly in disease states.

Pro-inflammatory cytokines secreted by activated microglial cells (which increase in number post-irradiation), including IL-6, IL-1-alpha and TNF-alpha, inhibit neurogenesis via a specific blockade in neuronal differentiation, as well as a nonspecific increase in precursor cell death (Monje et al., 2003).

Preventative Strategies & Therapies for Neurocognitive Decline in Children

There were no official clinical guidelines (NICE or otherwise) available for RT-induced neurocognitive sequelae management while this review was being composed. Hence the following is a collection of potential interventions that are being studied in clinical trials or in preclinical models.

Advances in RT Technology

Use of 3-D planning and intensity-modulated radiotherapy may help to prevent damage to critical neural structures (Belka et al., 2001). The use of fractionated cranial radiation therapy to deliver a greater number of small doses effectively (albeit incompletely) reduces toxicity to surrounding tissue. Stereotactic radiosurgery precisely targets a tumor by the use of very high-resolution neuro-imaging scans coupled with 3D computer-guided radiotherapy, so that the beam of ionizing radiation converges on the tumor while surrounding tissues receive only minimal exposure (Askins and Moore, 2008). Recent phase II clinical trials have shown promising results for the use of conformal hippocampal avoidance technology when delivering RT to the brain. Such hippocampus sparing attempts to avoid highly proliferative regions of the brain and directly targets tumours (Gondi et al., 2014; Gondi et al., 2010). The main disadvantage to this therapy is the suggested increased risk of incomplete ablation of cancer cells in certain regions. Another promising therapy - proton beam radiotherapy - involves almost all of the RT energy being focused onto the tumour, thereby sparing surrounding tissues of most toxic effects. This may not however be an appropriate treatment modality in all CNS cancers.

Pharmacological Interventions

Pharmacological interventions ideally should maximize brain function and minimize further damage. They can prophylactic, mitigating or treating in nature and are classified according to the time-points in which they are delivered (Moulder and Cohen, 2007). Most currently available pharmacological therapies are agents used to treat post-RT brain injury and include stimulants such as methylphenidate, acetylcholinesterase inhibitors like donezepil and the NMDA-receptor blocker memantine (Rooney & Laack, 2013). These drugs operate by altering neurotransmitter levels in the brain and are prescribed to alter cognitive function and attention post injury - with some effect. However they fail to address the apparent root of the problem - which a wealth of convincing data suggests is the neurogenic niche.

Take home points

- With improved childhood cancer diagnostic tools and therapies available, an increasing number of young patients are surviving CNS malignancies.
- Cranial irradiation is a mainstay of CNS anti-cancer therapy and often results in late and progressive neurocognitive dysfunction in both adult and younger patients being treated for primary CNS or metastatic cancers.
- Studies suggest that the underlying reason for the manifestation of late neurocognitive symptoms is a disturbance in the proliferative stem cell niches of the brain.
- Few (if any) effective therapies are available to treat the long-term neurocognitive side effects that result from the anti-cancer treatments patients receive.
- Preventative strategies for treatment induced cognitive decline including refined RT techniques and pharmacological interventions are being investigated but are yet to reach the clinic.
- To ultimately improve quality of life outcomes for patients, greater attention should be paid to cancer survivorship, in both the clinical and biomedical research settings.

Inflammation has been associated with reduced neurogenesis and administration of molecules that inhibit the production of pro-inflammatory cytokines by glia, such as microglia (e.g. minocycline), has attenuated this effect in animal models (Ekdahl et al., 2003). Other groups have shown that neuroinflammation alone inhibits neurogenesis and that inflammatory blockade with indomethacin, a common non-steroidal anti-inflammatory drug, augments neurogenesis after cranial irradiation (Monje et al., 2003). Given the breadth of evidence available to support the assumption that brain irradiation causes NPC loss due to the production and maintenance of a chronic inflammatory environment in the DG, it would stand to reason that local anti-inflammatory agents administered at different time points relative to radiation therapy should be investigated. Additional preclinical safety data are needed to ensure that calming the microglial response does not adversely affect tumor treatment efficacy.

Finally preclinical animal models support the use of lithium as a neuroprotective agent in the context of cranial irradiation. Lithium treatment protects irradiated hippocampal neurons from apoptosis and improves cognitive performance of irradiated mice. Lithium - more commonly associated with the treatment of psychiatric illnesses including bipolar disorder - has been shown in animal models to prevent neurocognitive deficits resulting from cranial irradiation (Yazlovitskaya et al., 2006; Zanni et al., 2015).

Stem Cell Transplantation

Animal brain irradiation experiments suggest that a depleted pool of DG neural precursor cells is the underlying reason for the development of neurocognitive difficulties over time - which then highlights the possibility of transplanting allogeneic neural stem cells into the injured brain to preserve function (Monje, 2008). Modulation of the recipient pro-inflammatory hippocampal microenvironment would have to occur before transplants to enhance transplanted precursor cell survival.

Behavioral Rehabilitation

Cognitive or behavioral remediation may provide benefit in attention, verbal memory, and mental fatigue. Programs consisting of developing new strategies to use intact cognitive pathways to perform impaired functions in new ways may improve the overall quality of life of patients in which all other available treatment modalities are contraindicated. Patients with the most severe impairments may not benefit from behavioural therapy due to cognitive deficits limiting the production of compensatory strategies (Askins and Moore, 2008).

A Need for Better Strategies

Finding a silver bullet strategy to target cognitive symptoms in the entire childhood CNS cancer survival population is highly unlikely. Differences between patients - with regard to tumour type, additional co-morbidities and concurrent therapies alongside RT - presents a highly heterogenous population to the biomedical scientist and to the oncologist. The biomedical scientist must thoroughly investigate as many neuroprotective avenues as possible and estimate clinical benefit. Meanwhile the clinician must decide what the optimal treatment is for childhood CNS cancer patients on a case-by-case basis. Personalised medicine - i.e. treatment tailored to an individual - is extremely fitting in this population. Ultimately it is down to the clinician's reasoning - based on the evidence placed in front of them in the form of a patient - to decide what strategy is required to maximize both survival and positive neurocognitive outcomes post-therapy. This places a lot of responsibility on the shoulders of the clinician and thus, requires the development of tools (mathematical models and advanced imaging techniques (Peiffer et al., 2013; Pospisil et al., 2015)) to predict the outcomes of each child's therapy and likelihood of cognitive decline. In order for oncologists to perform better and successfully treat cancer patients, they need more tools at their disposal.

Conclusions

Preserving neurocognitive function and childhood cancer survivor quality of life is becoming an important target in clinical trials as well as in daily practice. For progress to be made in the treatment of survivor cognitive comorbidities, the anatomy and biology of the neurogenic niches of the brain must be considered in the use of RT as a treatment or in protecting against or treating an RT-mediated insult. Therapies that help to protect or restore function in the hippocampus are fundamentally important in modern medicine. If the severe late effects of radiotherapy can be reduced, the overall quality of life would be greatly improved for the increasing number of children who survive CNS cancer. Specific diagnostic,

predictive and therapeutic tools need to be added to the clinician's arsenal so that they can further refine the balance between improved patient survival and acceptable toxicity and thus, ensure that children not only survive CNS cancers but also have the opportunity to live a normal life and achieve age-matched goals post-therapy.

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