Title: Leptomeningeal malignancy of childhood: sharing learning between childhood leukaemia and brain tumour trials.

David A Walker[1]., Lisethe Meijer[2]., Beth Coyle[1]. & Christina Halsey[3]

[1]Children's Brain Tumour Research Centre, University of Nottingham, School of Medicine, Queen's Medical Centre, Nottingham, NG7 2UH

[2]Department of Paediatric Neuro-Oncology, Prinses Maxima Center for Paediatric Oncology, Postbus 113, 3720 AC Bilthoven, Netherlands

[3]Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Garscube Estate, Switchback Road, Bearsden, Glasgow G61 1QH

Corresponding Author: Professor David A Walker, University of Nottingham, David.walker@nottingham.ac.uk

Summary (200 words)

Leptomeningeal malignancy (LM) complicates childhood cancers including leukaemias, brain tumours and solid tumours. In leukaemia it is assumed that the malignancy invades the leptomeninges via the vascular route. In brain tumours dissemination from the primary tumour, before or after surgery via the CSF pathways is assumed. However, there is evidence to support the vascular route of dissemination. Success in treating LM represents a rate-limiting step to cure, which has been successfully overcome in leukaemia with intensified systemic, combined with intra-CSF therapy, replacing cranial radiotherapy for the majority. This de-escalated CNS directed therapy is still associated with a degree of neurotoxicity. This balanced benefit justifies exploration of ways to further de-escalate CNS directed therapy. In primary brain tumours standard therapy rely upon cranio-spinal radiotherapy with the attendant risk of acute and delayed brain injury and endocrine deficiencies compounding post radiation impairment of spinal growth. Alternative ways of treating the lepto-meninges by intensifying drug therapy delivered to the CSF are under investigation. Preliminary evidence suggests improved outcomes. This review seeks to describe the methods of intra-CSF drug delivery, the current drugs in use and consider how the technique may be modified and additional drugs might be selected for this route of administration.

Key Messages

- Cancer affects 1:300 young people by age 20, <60% of whom have leptomeningeal involvement.
- In leukaemias, CNS directed therapy without cranial radiotherapy, has been successful in treating leptomeninges with reduced brain and endocrine consequences for survivors, further de-escalation of CNS directed therapy is being considered
- In brain tumours, cranio-spinal radiotherapy is effective but extremely toxic. Intensifying drug therapy with intra-CSF drug delivery is being explored with promising results.
- Intra-CSF drug delivery in brain tumours is complicated by post-operative changes and the co-existence of ventricular peritoneal shunts.
- Exploring alternative ways of delivering intra-CSF drugs and expanding the range of drug suitable for this purpose are necessary to allow the potential benefits to be offered to all.

Conflict of Interest

The authors declared no conflicts of interest

Background

Cancer affects 1:300 people by aged 2 years, at least two-thirds of whom present a risk of leptomeningeal involvement (LMI) [Charles Stiller, Personal Communication]. When it occurs, it is a rate-limiting step for cure thereby presenting a challenge to the therapist especially in primary brain tumours where the risk of LMI is greatest. Historically, craniospinal radiotherapy has been the standard approach to treating the risk of, and actual LMI, complicating brain tumours. Indeed, it offered the first examples of "cure" in medulloblastoma (1,2) .

Aggressive pre-emptive treatment of LMI has been a routine component of treatment for childhood leukaemias and high-grade lymphomas since the 1970s and is considered essential for cure. Initial use of central nervous system (CNS) targeted radiotherapy was associated with unacceptable long-term cognitive and adverse endocrine effects leading to gradual phasing out of its routine use in first-line therapy. It has largely been replaced with intensified systemic and intra-cerebrospinal fluid (CSF) therapies. Despite this, CNS-directed therapy remains potentially toxic, with a lack of reliable biomarkers to guide risk-adapted therapies. Thus, the challenge in haematological malignancies is reducing the toxicity of CSF-delivered drug regimens in first line treatment without compromising efficacy.

Risks of radiation therapy to the brain

Extended fields of high dose radiotherapy early in life carry heavy penalties for brain development, affecting the development of normal cognition and memory, limiting spinal growth and damaging endocrine function (particularly growth hormone). The risk of second malignant and benign brain tumours is particularly worrying in disease groups where cure rates now exceed 70% at 5 years and beyond. Scatter dose radiation to non-CNS tissues in the neck, thorax and abdomen increase the volumes of tissue at risk of second tumour development after radiation damage. These penalties are greatest when used in the youngest children with the most tissue development and growth to follow (3). The modification of radiation fields using Intensity-Modulated Radiation therapy (IMRT), tomo-therapy and proton therapy offer reductions in scatter dose radiation and greater precision of tumour bed volumes but cannot compensate for the radiation brain injury within boosted fields, consequent upon cranio-spinal radiotherapy (3,4). The balance of benefits and risks therefore have been difficult to judge in primary brain tumours, in contrast to leukaemia and lymphoma, because the brain needs to be treated vigorously to eradicate the primary tumour with surgery, radiotherapy and possibility of safely reducing the risk of radiation brain injury. Progress has been slow in clinical trials because of the diverse primary brain tumour groups, where optimizing curative therapy in high risk disease was initially prioritized in trial design; subsequently, trials were directed at de-escalating radiation dosing and field volumes by introducing clinical and molecular risk stratification and compensatory systemic chemotherapy (4).

CSF therapy in Brain Tumours

A recent trial has identified that CSF etoposide (0.25-1mg) given to children and young adults with malignant brain tumours can be combined safely with systemic chemotherapy and radiotherapy using daily or twice daily bolus administration over 5-10 days every 2-5 weeks (5)(Ref). There have also been reports of the use of intra-ventricular –methotrexate in patients with metastatic, relapsed or refractory medulloblastoma, which was well tolerated. A meta-analysis identified a correlation between cumulative intra-ventricular methotrexate dosing and improved outcome (6,7). A single arm study in highly malignant atypical teratoid rhabdoid tumours (ATRT) included the use of intra-CSF Cytarabine, methotrexate and hydrocortisone (8) and another is testing intra-CSF Etoposide and Topotecan/ Depocyte® as part of an anti-angiogenic multi-agent regime in relapsed medulloblastoma (8,9). A meta-analysis of intra-ventricular therapy found that intra-ventricular therapy contributed to enhanced survival in Atypical Teratoid Rhabdoid Tumour (ATRT) (10). An international randomized trial investigating the role of CSF delivered methotrexate, in pre-school age children with low risk medulloblastoma was about to be launched but is being reconsidered as a result of the early closure of ACNS 1221 trial (11), which excluded ventricular therapy from the regimen demonstrating an excess of relapses compared to a similar chemotherapy study including intra-ventricular methotrexate. The SHH biological sub-group in this trial had favourable outcomes and the role of different adjuvant

strategies are currently being considered for randomized comparisons where intra-ventricular therapy may be part of the strategy selection (12,13). There is growing evidence therefore that intra-ventricular therapy with the historical drug methotrexate and other drugs can contribute to enhanced outcomes in higher risk malignant tumours types.

Novel methods of CSF drug formulation, delivery or scheduling have not been explored. Possible restraining factors include the rarity of the clinical problem in children compared to adults, where 1:2 people are at risk of cancer and 40% are at risk of LMI. There is also a need to test new systems in children, and the added cost and challenge of international collaboration and pharmaceutical engagement. The scene is set therefore for further investigation of CSF delivered therapy in primary brain tumours, to both enhance tumour control and reduce neurotoxicity in risk-adapted therapies

In this review, we will re-consider the potential for CSF delivered drug therapies in childhood malignancies and discuss how optimization of CSF drug delivery might be explored in future trials of both CNS and haematological malignancies. We will consider haematological malignancies first, as the most progress has been made with these to date.

Leptomeningeal infiltration in haematological malignancies

LMI complicating haematological malignancies is a diffuse and/or multifocal invasion of the leptomeninges at the vascular-meningeal interface (14). Leukaemic blasts are thought to reach the leptomeninges by the vascular route, crossing the blood-CSF barrier, or by direct extension along bridging veins from the adjacent skull and vertebral bone marrow (figure 1) (15,16).

Several lines of evidence suggest that LMI in ALL is significantly underdiagnosed using conventional cyto-morphology (cytospin) and is likely to be present in most children at initial diagnosis (16–18). Indeed, the introduction of universal CNS-directed therapy, irrespective of initial cytospin findings, led to a dramatic improvement in overall survival (OS) from 20-30% to 50-60% in the 1970's (19). Initially radiotherapy was used to treat LMI but high rates of secondary CNS malignancies and endocrinopathies led to a switch to targeted treatment with intensified methotrexate or triple intrathecal therapy (methotrexate, cytarabine and steroids), alongside systemic drugs with good CNS penetration. This approach has reduced CNS relapse to less than 5% and increased OS rates >90% (20). However significant methotrexate-related neurotoxicity still occurs. Acute neurotoxicity includes headaches, somnolence, seizures, or methotrexate "stroke-like syndrome" (19). In addition, methotrexate has been implicated as one of the causative agents for chronic neurocognitive defects seen in up to 50% of children

post ALL therapy ((21,22)). Efforts are now concentrating on reducing the burden of CNS-directed therapy by improved systemic control, and more sophisticated methods to monitor the response of LMI to the delivered therapies to allow tailoring of treatment intensity to a child's individual risk of CNS relapse. Refractory and/or relapsed CNS leukaemia can be very challenging to treat and novel agents with a reduced toxicity profile for these heavily pre-treated patients would be advantageous. These include liposomal cytarabine and immunotherapies such as CAR-T cells and bi-specific antibodies.

Leptomeningeal infiltration in primary brain and other solid tumours

LMI has a similar pathological appearance in primary brain malignancies. In medulloblastoma, the commonest childhood malignant brain tumour, 30% present with LMI (23) and 60% have LMI at relapse (24). All are treated assuming LMI is a risk. A recent study by Zapotocky et al. has however suggested that group 3 tumours tend to show laminar (diffuse) metastatic dissemination, group 4 tumours show a mixture of laminar and focal metastases and sonic hedgehog tumours are associated with multifocal lesions. Thus, the pattern of metastasis appears to be linked to the underlying molecular drivers of the disease and may also link to outcome (25). LM disease has been found to differ in its molecular profile from the primary tumour suggesting clonal selection as part of process of dissemination (4,26–28). Thus, metastatic tumours have either diverged prior to treatment or been selected and expanded as a result of treatment. In either case, the resultant

leptomeningeal metastasis has genetically diverged and is unlikely to respond to same targeted treatment as the tumour of origin. Leptomeningeal dissemination has traditionally been hypothesized to be via the CSF whereby cells enter the CSF at the tumour : CSF interface or after surgical disruption during tumour resections. Recent evidence has, however, identified that there may be a proportion of cases where tumour cells reach the LM via the vascular route as in leukaemia / lymphoma (29,30). These alternatives routes of dissemination to LM would justify the use of both systemic and CSF delivered drugs in their prevention and treatment. Although not necessarily the same targeted drug since both may have evolved.

Treatment Considerations

Cytotoxic concentrations in the CSF of systemically administered drugs are compromised by the blood-brain-barrier and blood-CSF barrier. Drug transfer from blood to CSF is compromised by tight junctions between the capillary endothelial cells (31,32). This barrier can be overcome by choosing drugs with specific physical and pharmacological characteristics including: low molecular weight (<500 kDa), high lipid solubility (33), structures with few nitrogen and oxygen atoms (preferably <8-10), small physical size <11 nm, low protein binding and hydrogen bonding (33). Drug penetration of CSF is also inhibited by drug influx and efflux transporters, increased interstitial pressure of brain and tumour and reduced blood flow in the tumour (34). Intra- and extracellular enzymes may inactivate or be required to activate compounds.

One approach to this poor penetration of drugs into the CSF is to use exceptional systemic dosing such as high dose methotrexate with folinic acid rescue in leukaemias (35) or high dose multi-agent chemotherapy with stem cell rescue in brain tumours (36) to try and achieve higher concentrations of cytotoxic drugs within the CNS. Alternatively, intra-CSF administration is a method to circumvent these barriers, as was observed in a study in brain tumour patients where systemic HD-etoposide (400 mg/m^2 over 96 hours) was administered as part of intensified systemic therapy. This schedule failed to achieve a cytotoxic CSF concentration (>0.1 µg/ml) (37), whilst the same drug Etoposide administered into CSF at 0.5 mg daily for 5 days achieved a CSF concentrations at more than 100-fold the level achieved by systemic administration with negligible systemic or CNS toxicity.

The successful use of intra-CSF therapy in childhood leukaemia / lymphoma is notable. Although the choice of agents that are suitable for intra-CSF delivery and also effective against leukaemia has severely limited the selection of drugs for testing in primary brain tumour indications, The only new drug in the past four decades developed for this route of administration is liposomal cytarabine (Depocyte®). On the one hand, it has an attractive pharmaceutical profile because of its sustained release pattern reducing the need for repeated lumbar puncture; on the other hand, arachnoiditis side effects requiring concomitant steroids, coupled

with its high cost and complex manufacturing process has resulted in its recent withdrawal from the market (38).

The lack of new drug development has led researchers to explore existing chemotherapy agent's suitability for administration via the CSF, mainly off license. Their selection being justified by pharmacological principles and published evidence. Shortlists of existing agents have been drawn up for primary brain tumours and preliminary trials of their use have been reported (39). A key feature has been to select drugs with no evidence of neurotoxicity, as direct administration to the CSF will bring the drug into direct contact with brain at CNS concentrations exceeding that achieved by systemic routes. Using this approach, methotrexate was excluded as a suitable candidate because of the extensive evidence of its neurotoxicity especially in previously irradiated patients. A UK national guideline has specified intra-CSF methotrexate in favourable risk medulloblastoma in pre-school age children (13,40). Neurotoxicity of this approach is, therefore, anticipated but may be difficult to attribute to the drug as opposed to the toxicity of delayed diagnosis, surgical interventions and systemic chemotherapy (41). This could be the focus of future randomized trials.

Optimising LM-directed drug therapy

The requirements for LM-directed therapy are: maintaining an optimized therapeutic concentration at the tumour site, with acceptable systemic and

neurotoxicity (42) to eradicate tumour cells in order to stabilise tumour-related neurological signs, while maintaining quality of life and, where highly effective, prolonging survival (43).

To optimize intra-CSF chemotherapy efficacy, CSF flow characteristics and drug pharmacokinetics need to be taken into account.

CSF distribution volume is static in children over 3 years of age at 110-150 ml (44). Intraparenchymal penetration of intra-CSF administered drugs is limited to 2-3 mm (45). Characteristics favouring CSF drug delivery include direct contact with tumour cells, small CSF volume of distribution and the absence of a first pass effect. This allows very low drug dosages to achieve cytotoxic levels in the CSF, thereby avoiding systemic toxicity.

CSF velocity, and therefore speed of mixing and dissemination of drug administered to CSF spaces, is determined by the choroid plexus flow. This is amplified by a pulsatile CSF motion (caused by blood flow and breathing pattern) (46) at an average of 0.35 mL/min (34), occupying the entire CSF space in 5-7 hours (47), thus exchanging the entire CSF volume four times a day. This is referred to as bulk flow. The clearance rate limits drug-to-tumour exposure time, which theoretically could compromise the efficacy of cell-cycle dependent drugs such as

MTX, etoposide and cytarabine. Solid tumours have slower proliferation rates where prolongation of contact between drug and tumour would be theoretically advantageous.

Where physiological CSF flow is from choroid plexus in lateral, third and fourth ventricles to the arachnoid granulations in the superior sagittal sinus, the most efficient administration route is by intra-ventricular route with the drug flowing with the CSF bulk flow. This route of administration requires an intraventricular catheter such as an Ommaya reservoir. This is an implantable device consisting of a small capsule situated between the skull and overlying scalp connected to a catheter communicating directly with one of the lateral ventricles (48–50).

This permits painless access to the ventricular CSF for both sampling and drug administration. Infection can be controlled, but not excluded, by meticulous aseptic technique. Case selection requires a clear understanding of CSF flow patterns around the CSF spaces. This has been compared favourably to the intralumbar route in studies with MTX (51), mafosfamide (52) spartaject busulfan (53), and topotecan (54,55). Furthermore, lumbar injections are often unknowingly misplaced leading to ineffective delivery to the CSF (56). It has been demonstrated that lying flat after lumbar puncture optimizes drug distribution to upper half of the spinal cord. Intensification of lumbar administration by daily delivery is used but

unpopular because of local discomfort with repeated lumbar puncture and, in children, the requirement for sedation or anaesthesia (19).

It has been hypothesized that the pharmacokinetics of the drug delivery to CSF would be best optimized by continuous infusion as opposed to bolus administration (34). A bolus administration achieves a peak concentration, followed by washout by CSF bulk flow over time. A continuous infusion would reach a plateau drug concentration throughout CSF spaces. Such an approach requires an administration device offering stable prolonged intra-CSF drug access with a portable continuous infusion pump (34) suitable for children of all ages (57). In post-operative states additional consideration needs to be given to the impact of raised intra-cranial pressure, meningitis or proteinaceous CSF interacting with CSF concentration and circulation / distribution of intra-CSF drug (58).

Despite these considerations, the standard approach to intra-CSF drug administration for leukaemia lymphoma is intermittent lumbar injection frequently under anaesthesia. The frequency of administration is intensified where frank CNS disease is seen on CSF sampling. Standard protocols deliver intra-CSF therapy at weekly to monthly or 3-monthly intervals. The efficacy of such intervals coupled with the brief presence of the drug in the CSF due to its removal by bulk flow has not been studied pharmacologically to justify this approach. Its introduction, in combination with intensified systemic therapy to replace more damaging CNS

radiation, justified the empirical adjustment to protocols (59). Multi-centre clinical trials concluded that sustained use of intra-CSF therapy without cranial radiotherapy offered acceptable CNS- relapse rates (60–62). Intrathecal therapy offers much lower rates of neuroendocrine problems and secondary tumours than craniospinal irradiation. However, prolonged intra-CSF methotrexate and/or triple therapy has been associated with adverse neurocognitive and neurobehavioural outcomes (63) and concerns are emerging about possible "accelerated aging" in the CNS 20-30 years post therapy (64).

The use of intraventricular (Ommaya reservoir) delivery of CNS-directed therapy in childhood ALL has declined over the years despite early literature , mainly from the 1970's, reporting superior pharmacokinetics, its ease of use, and possibly increased efficacy compared to conventional lumbar delivery (65) (64). It should be noted that no randomised controlled trial of intrathecal vs intraventricular therapy has ever been performed in ALL and the literature consists of small mixed case series mainly from the 1970's and 1980's (56). The decline in use of Ommaya reservoirs may have been due to concerns about its usual placement for life and the risks of CNS infection, although meticulous neurosurgical and aseptic technique has reduced these risks considerably (56,66,67).

Hydrocephalus / Ventricular shunting

For these reasons, we propose that protracted CSF infusions monitored by CSF sampling of drug concentration would be a preferable strategy in patients with shunts, a stable CSF drug concentration may be achieved allowing equilibration across the CSF spaces as long as there are no isolated cavities (figure 2). Where even distribution cannot be guaranteed, CSF flow studies prior to intra-CSF drug administration with either ^{111}Indium-diethylenetriamine penta-acetic acid, ^{99}Tc macro-aggregated albumin, or gadolinium (47,68–70) may be warranted, since standard MRI imaging might be insufficiently sensitive to assess flow characteristics in detail (69). Surgical intervention in adults has been proposed to remove bulky disease and restore CSF flow, which has been shown to prolong survival, lower treatment related morbidity and death rate from LMI (68,71,72) We are unaware of such surgical interventions being adopted in children.

Drug selection for intra-CSF delivery

Methotrexate is the most commonly used intra-CSF chemotherapy agent. This is largely due to its position as one of the first effective therapies for leukaemia in the 1950's and 1960's, rather than a critical evaluation of potential efficacy and toxicity profiles of a variety of alternative intra-CSF agents. In fact, using modern criteria, the neurotoxicity profile of methotrexate makes it an unattractive first choice agent for intra-CSF delivery. Despite this, it has repeatedly been shown in large scale RCTs to be an effective drug for prevention of CNS relapse (60–62,73) and therefore remains widely used in ALL and lymphoma protocols (19).

Since intra-CSF therapy for brain tumours is in its infancy, there is a great opportunity to move away from methotrexate to alternative less toxic intra-CSF agents. Conroy et al (39) defined a number of required drug properties for intra-CSF administration:

1. Clinical property:
    - Non-irritant
    - Neurotoxicity low or absent
    - Evidence of tumour sensitivity
2. Biological property:
    - CSF transport system absent
    - Cell cycle non-specific drugs
3. Physiochemical and pharmaceutical properties:
    - Active in CSF
    - Hydrophilic and/or ionised at CSF pH therefore low membrane permeability (to minimise diffusion out of CSF)
    - Molecular size (>700 kDa)
    - Suitable formulation readily available

Taking these characteristics into account Depocyte® –(liposomal cytarabine, slow release formulation), mafosfamide (cyclophosphamide analogue), and etoposide were selected as suitable candidates for intra-CSF treatments suitable for trial in medulloblastoma (panel). Depocyte® –and mafosfamide can cause chemical

arachnoiditis (fever, nausea, vomiting, headache, and back pain) (74,75), justifying concomitant dexamethasone (0.15 mg/kg/dose IV or orally, twice a day for 5 days) (76–78), or low infusion rate (maximum 1 ml/min) (52). However, they have both now been withdrawn from production and are unavailable (38). Depocyte® was withdrawn due to production difficulties, whilst Mafosfamide was never fully registered as a drug and its manufacture was discontinued.

Other complications are transient such as headaches (37,43,74,79), infections of intra-CSF administration devices in <10% of patients (37,43,74,80), nausea and vomiting, seizures, and confusion (79,80). Symptomatic subacute leukoencephalopathy (confusion, somnolence or irritability, ataxia, dementia and tremor or myelopathy are rare events (37,43,79), and are more common with concurrent systemic treatment and/or radiotherapy (81–85), or CSF flow obstruction (68,69),

Use of systemic immunotherapies to target leptomeningeal infiltration

Recent advances in immunotherapies have opened up new treatment approaches for relapsed/refractory LMI in ALL. Systemically delivered chimeric antigen receptor T cells (CAR-T cells) have been shown to home to the CNS and produce long-term remissions in patients with CNS-relapses (86). Indeed, excellent CAR-T cell expansion has been demonstrated in CSF following IV administration (87). Novel bi-specific antibodies, such as Blinatumomab (88), also have proven efficacy

against CNS leukaemia. It is worth noting that these therapies are also associated with significant neurotoxicity although the exact mechanisms of this, and whether they relate to the presence of LMI or systemic cytokine release, remains unproven (89,90). In addition, other barriers to widespread adoption of immunotherapy for LMI in ALL are large treatment costs and the current lack of effective agents against T-ALL (which has higher rates of refractory LMI than B-ALL).

When evaluating new products, the degree of CNS-homing of different classes of immunotherapy should be taken into account. In contrast, to CAR-T and bispecific antibodies, NK-based therapies (91) and monoclonal antibodies such as Rituximab may not be able to cross into the CSF without direct intra-CSF delivery (92).

The application of immune strategies in brain tumours is in early development preliminary experience is limited to exploration of the use of intrathecally delivered immune-stimulants such as Interleukin 2 and interferon beta (93). Intraventricular administration of radio-immunotherapy using (131) I-3F8 in medulloblastoma has been shown to be safe and feasible and could be used to complement other therapies in the future (94).

Future directions for treatment of LMI

Haematological malignancies

Interestingly, the use of intra-CSF therapy for haematological malignancies and brain tumours appear to be going in opposite directions. In haematological malignancies, the focus is on optimising the use of systemic drugs with good CSF penetration and concomitantly reducing the burden, and, potentially, the toxicity of intra-CSF therapy. Whereas in brain tumours, judicious use of CSF directed therapy for LMI is gaining importance with an associated focus on other CNS directed drug delivery techniques to try to enhance efficacy of drug therapy for primary brain tumours.

Despite this, many opportunities for advances in treatment of LMI in ALL exist. Firstly, sensitive biomarkers need to be developed to allow accurate detection of LMI and to track its response to initial CNS-directed therapy. Once available, future studies would be able to use these biomarkers to test de-escalation of CNS directed therapy for patients at low risk of CNS relapse, thus significantly reducing their exposure to currently used neurotoxic agents. A move away from methotrexate to either less neurotoxic cytotoxic agents such as cytarabine, etoposide, topotecan or carboplatin, or newer targeted, non-neurotoxic treatments for intra-CSF delivery would benefit all patients, but the immense difficulties in switching from an efficacious (albeit toxic) agent to an unproven novel agent are not to be underestimated.

Advances in this area are likely to be seen by testing existing previously unused agents via the intra-CSF route as well as novel agents, as bolus or infusional therapy, in cases of relapsed or refractory disease. The point of drug delivery may need to be reconsidered. Although, systemic immunotherapy may prove to be the first-line choice in leukaemias it will be limited by cost, toxicity and lack of efficacy against T-ALL.

CNS malignancies

In brain tumours, taking the lead from haematological malignancies, the priority is to sustain control of LM disease whilst reducing the burden of morbidity and late consequences particularly of radiation therapy to the cranio-spinal axis. One way this could be achieved would be to establish devices and techniques to deliver infusional intra-CSF therapy and explore the most suitable existing and new agents emerging from research and development for this route of administration. Ninety percent of new cancer drugs do not cross the blood brain barrier sufficiently for an effect to be anticipated by systemic administration. Such drugs delivered directly to the CSF may have a much greater impact. Their exploration in trials via the intra-CSF route should be prioritized involving children with specific requirement to avoid the serious neuro-toxicity of cranio-spinal radiotherapy in pre-school age children and in children with relapsed disease initially, once feasibility of intra-CSF administration is established.

Priorities for future research

Perhaps the most important developments is a commitment to identify new effective and less toxic drugs, and safe and easy systems for their delivery, to target malignancies in the LMI. The proposed infusional intra-CSF studies are being pursued with the intent of developing a platform for their testing and selection of drugs for further development. Sustained release systems such as Depocyte® offered a sustained profile after a single injection. An expanded range of such preparations with targeted agents is an attractive prospect. Sharing delivery systems and target selection with the needs of adult practice would create synergy for their commercial development.

Search strategy and selection criteria

Relevant literature was identified using PubMed and article reference lists. Search terms comprised leptomeningeal, paediatric, adolescent, cancer, leukaemia, brain tumour, medulloblastoma, cerebrospinal fluid and drug-delivery. Search was restricted to English language with no date restrictions

Author contribution:

CH - Performed literature search and contributed to writing of manuscript

LM – Performed literature search and contributed to writing of manuscript

DAW – Conceived of the need for the review and contributed to writing of manuscript

BC – Contributed to writing of manuscript

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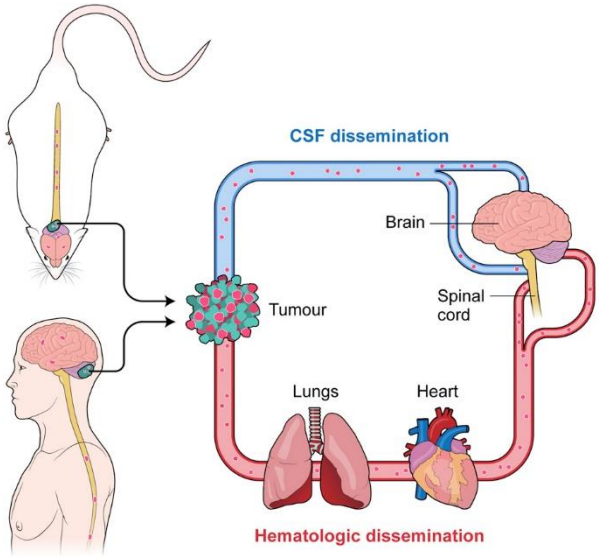

Figure 1: Mechanisms of leptomeningeal dissemination from primary brain tumors via CSF or haematogenous routes

Adapted from ref 29. **[Note: this is from Cell (published by Elsevier) and open access, so no need to ask for permission. We will remove the mouse and change the adult to a child]**

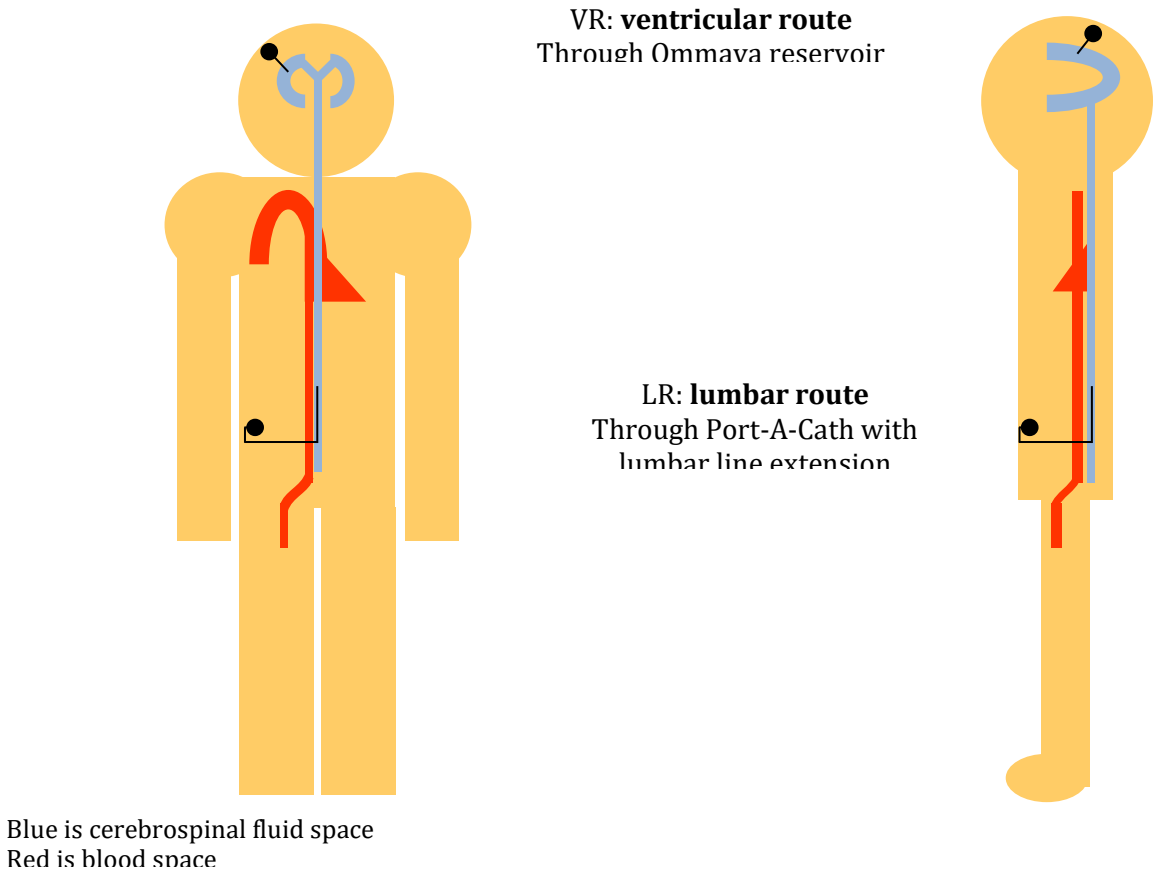

Figure 2: Routes of administration for intra-CSF therapy (VR - ventricular route; LR – lumbar route). LR can be used in patients with ventriculoperitoneal shunts

Panel: Drugs graded by eligibility for trial by intrathecal administration for medulloblastoma (ref 37 - Conroy et al 2010)

Agents under trial

Liposomal cytarabine (Depocyte®)*
Mafosfamide*

Agents suitable for clinical trial

Carboplatin
Etoposide

Nimustine (ACNU)

Drugs requiring further investigation before clinical trial

Floxuridine (FDUrd)
4-hydroperoxy-cyclophosphamide

Drugs requiring further investigation, lower priority

Diaziquone
Mercaptopurine
Rubitecan
Topotecan
Radio-immunotherapy ^{131}I-3F8 murine monoclonal antibody

Drug with insufficient information to grade

Temozolomide

* This drug has now been withdrawn from production by the manufacturer