Medulloblastoma in childhood: revisiting intrathecal therapy in infants and children

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Abstract

Introduction: Intrathecal chemotherapy is being explored in medulloblastoma in pre-school children as part of brain-sparing strategies and as an alternative to unacceptably neurotoxic cranio-spinal radiotherapy. The range of drugs suitable for this route of administration is restricted by the lack of research evidence of pharmacological suitability and efficacy of other drugs in medulloblastoma.

Methods: Ideal clinical, biological, physicochemical and pharmaceutical properties for intrathecal administration were defined through literature review of pharmaceutical texts, Medline, Embase and consulting the manufacturers. 126 chemotherapy agents were assessed against these criteria by searching the academic domain of pharmaceutical texts, computer databases and consultation with manufacturers.

Results: Of 126 candidates drugs, 99 were rejected because of documentation of their irritant nature, neurotoxicity and requirement for hepatic activation in standard pharmaceutical texts. Fifty were rejected for a single identifiable reason including, neurotoxicity (n=24), irritant (n=15), needs enzyme activation (n=5), clinical evidence of intrathecal neurotoxicity (n=4) and no evidence of tumour-specific efficacy (n=2). Where two reasons were cited the justifications were: neurotoxic and irritant (n=3) and needs activation and systemic administration results in equivalent concentration (n=1). Twenty seven drugs remained of which 12 were selected as eligible for further clinical investigation, and 15 were selected for further pre-clinical investigation.

Conclusions: The predetermined criteria were not applicable, in their entirety, in the majority of drugs, due to lack of information in the academic domain, emphasising the importance of a more open approach to sharing basic drug information. The prioritised list of 12 candidate drugs for clinical trial and 15 for pre-clinical investigation justify that a concerted research effort in this area of practice is made. (317 words)

Introduction

Medulloblastoma, the commonest malignant CNS tumour of childhood [125], has the capacity to disseminate through the lepto-meninges, presenting at diagnosis or at relapse after treatment. Leptomeningeal metastases (LM) grow at the interface of the brain and spinal fluid. They are thought to occur as a result of interplay between operative disruption of tumour cells contaminating the CSF and inherent biological capacity for tumour cells to migrate, adhere and invade neural tissue. Where LM are present at diagnosis biological factors are increasingly being associated with this dissemination and poorer cure rates with standard therapy. Systemic chemotherapy has an established role in medulloblastoma with evidence of chemosensitivity, enhanced survival rates and rising survival rates reported by trials groups and population registries [80] in recent eras.

The use of intrathecal chemotherapy in childhood leukaemia and CNS tumours has been the focus of reviews [17, 49, 108] and reports of phase 1 and 2 studies [17]. In leukaemia the intensification of systemic and intrathecal therapy has permitted exclusion of CNS radiotherapy for the majority of newly diagnosed cases with very low CNS relapse rates, acceptable late toxicity using methotrexate alone or in combination with cytosine and hydrocortisone. The intrathecal route in leukaemia has been demonstrated to bypass the blood brain barrier (BBB), enhance CSF drug concentrations reducing systemic exposure and, therefore, toxicity. Selection of drugs suitable for intrathecal administration and with evidence of sensitivity to primary CNS tumours is a challenge in medulloblastoma, therefore. Preliminary evidence of the efficacy of intrathecal therapy is emerging. Slavc reported extensive use of intrathecal therapy at relapse using etoposide, mafosfamide and others [120, 121]. Other studies report the feasibility of this route of drug administration at relapse and as part of palliative care with infrequent complications and prolonged symptom free intervals. Rutkowski reported very high survival rates in pre-school children treated with chemotherapy-only strategy including intraventricular methotrexate [109]. The proposal that intrathecal therapy be tested in a prospective European trial of medulloblastoma in this young age group is currently the focus of debate [139].

In order to further develop an enhanced evidence-base for the selection of drugs that are effective against medulloblastoma, suitable for administration by the intrathecal route, and non-toxic to the nervous system, we developed criteria for the ideal intrathecal agent. Following this a systematic literature review was conducted using these criteria to identify candidate drugs worthy of further trial for intrathecal use in medulloblastoma.

Method

Identification of candidate drugs

A comprehensive list of chemotherapy agents was extracted from a drug pharmacopoeia [87]. Properties of the ideal intrathecal drug were identified based upon literature review [4, 10, 13,

33, 53, 102, 108, 132, 136, 143, 150, 151] and grouped according to: "ideal clinical properties", "ideal biological properties" and "ideal physico-chemical and pharmaceutical properties".

Ideal Clinical Properties

Non-irritant

The drug would need to be non-irritant to avoid chemical arachnoiditis or meningitis. Any drug reported in any of our reference sources to cause irritation or thrombophlebitis was therefore eliminated from further consideration.

Neurotoxicity

Any drug given intrathecally has a significant risk of neurotoxicity. Evidence for neurotoxicity when given systemically or intrathecally was determined as an unacceptable risk for further evaluation of CSF administration. It was not possible to grade the neurotoxicities as they were variably reported. Some drugs which are not usually neurotoxic when given systemically at conventional doses, may be toxic if given intra-arterially, intrathecally or in very high doses [130]. Any drug reported in any of our reference sources to cause neurotoxicity was therefore eliminated from further consideration. Methotrexate and cytosine arabinoside, whilst suitable for IT delivery, have only been studied in medulloblastoma with concurrent systemic chemotherapy agents, the chemosensitivity of medulloblastoma to these drugs is, therefore, unknown.

Tumour sensitivity / mechanism of action

Evidence of activity of the drug against medulloblastoma, PNET or leptomeningeal carcinomatosis is required to warrant further investigation. A drug with a mechanism of action effective at the CSF/leptomeningeal interface would offer a therapeutic advantage.

Methotrexate and Cytosine Arabinoside

Interestingly, the strict application of these criteria led to the exclusion of methotrexate and cytarabine (in its standard formulation) from the list of potential candidates. We are aware that these agents are commonly used intrathecally. The application of 'ideal criteria' which identifies lack of chemosensitivity data and substantial evidence of neurotoxicity led to their rejection from our ideal list, for the purposes of this review.

Ideal Biological properties

CSF transport system

Some drugs are removed from the CSF by facilitated diffusion using carrier transport systems such as those for organic ions, quaternary ammonium compounds, organic bases and acids, also transporters conferring multi-drug resistance such as P-glycoprotein, multi-drug resistance protein 1, monocarboxylic acid and organic ion transporters [126]. The ideal

intrathecal agent will have no active transport system that is capable of removing it from the CSF.

Cell cycle non-specific agent

Cells in the process of dissemination may be in a non-cycling, G_o, or slow cycling phase. Drugs which act at specific stages of the cell cycle will need to be in contact with the cells for sufficient time for the cells to go through active cell division, to ensure an effective cell kill. An ideal agent would therefore be cell cycle non-specific in its action.

Ideal Physicochemical and pharmaceutical properties

Active in CSF

Drugs requiring enzyme activation (e.g. cyclophosphamide) are unlikely to be active since there are very few enzyme systems present in the CSF. Drugs administered in their active form or with predictable activation (e.g. hydrolysis) are proposed. Those requiring other processes of activation are excluded.

Factors affecting BBB permeability

Drugs in the CSF are likely to be in equilibrium with plasma as determined by the characteristics of the BBB and the drug's physical characteristics. Factors that reduce a drug's capacity to diffuse across the BBB and therefore limit drug efflux include: low lipophilicity, high hydrophilicity, ionised state at CSF pH of 7.3 and molecular weight >700 Da [53]. Such properties should therefore enhance sustained CSF drug levels and are therefore preferred for intrathecal therapy.

Protein binding

Ideally drugs normally protein bound are excluded from crossing the BBB due to molecular size, direct injection would overcome this and sustain their presence in CSF. This criteria has, however, not been used as the information was not available for the majority of drugs.

Formulation for CSF administration

The drug must be soluble in the appropriate concentration for intrathecal administration, and in a vehicle which is suitable for this route, including bio-compatibility with surgical delivery systems such as ventriculostomy reservoirs.

(Insert Table 1 here - Summary of clinical, biological and physicochemical / pharmaceutical properties used to justify selection or rejection of drugs)

Literature search strategy and selection criteria

An initial search for the properties of each drug on the candidate list was undertaken by screening standard pharmaceutical texts [9, 30, 87] and by consulting the manufacturer.

Some information was obtained from these sources. This permitted immediate elimination of a number of drugs due to evidence of irritancy, neurotoxicity and the need for liver enzyme activation. However details of ionisation state and degree of protein binding for many drugs was unavailable despite direct approaches to manufacturers.

For the remaining drugs, Medline (1966 - present) and Embase (1980 – present) searches were performed. Each drug name was separately combined with the following terms: 'medulloblastoma', 'PNET' and 'leptomeningeal carcinomatosis', used in the 'exploded' form. Where hits exceeded 50 for a combination of terms, the search was further narrowed by combining that search with 'intrathecal administration'. The full text of papers with relevant abstracts were obtained and physicochemical information was extracted as well as:

- evidence of the drug's activity against medulloblastoma, PNET and leptomeningeal carcinomatosis in vitro and in vivo
- absence or presence of neurotoxicity reported from systemic or intrathecal administration
- documentation of intrathecal administration in vivo and in vitro.

Results

One hundred and twenty-six drugs were initially identified for investigation. 35 were immediately rejected after consulting standard pharmaceutical texts where there was documentation of irritant qualities, neurotoxicity or the need for enzyme activation of a pro-drug. Literature searches for the remaining 91 drugs identified 33,627 hits. Screening of abstracts reduced this to 200 full papers which were read, justifying the rejection of a further 64 drugs (see Table 2a & b).

(Insert Table 2 here – List of chemotherapy drugs considered with selection / rejection status and rejection justification)

Rejected drugs

Of the 126 licensed and investigational anti-cancer chemotherapy agents identified, 99 drugs were excluded (Table 2a & b). In 45 cases rejection was due solely to the lack of information. The remaining 54 drugs were rejected for a single reason (n=50) or a combination of two reasons (n=4). Where a single reason is cited the justifications were: neurotoxicity (n=24), irritant (n=15), needs activation (n=5), neurotoxic when given intrathecally (n=4), lack of activity in relevant tumour type (n=2). Where two reasons were cited, the justifications were: neurotoxic and irritant (n=3), and needs activation and systemic administration results in equivalent concentration (n=1).

Prioritised drugs for intrathecal use

From our initial list of 126 drugs, 12 drugs have been identified as suitable for further testing by the intrathecal route in medulloblastoma. Fifteen other potential candidates lack sufficient information to currently justify exploration of intrathecal administration, but warrant further research. The 27 drugs are therefore candidates for further testing via the intrathecal route focussed upon in childhood medulloblastoma and other leptomeningeal malignancies.

The most promising 12 drugs for PNET/medulloblastoma with prior reported clinical experience are detailed in Table 3 with justification of their potential for future research.

(Insert Table 3 here – Drugs currently eligible for consideration for trial by intrathecal administration for medulloblastoma)

Evaluation in progress

Liposomal cytarabine and mafosfamide are currently undergoing phase 2 trials by the intrathecal route in children with brain tumours with leptomeningeal spread. Liposomal cytarabine has now been associated with significant neurotoxicity, particularly in adult patients also treated with systemic cytarabine [16]. It may be better tolerated in children. Comitant systemic corticosteroid treatment is recommended. Further studies are needed to establish optimal use of this drug.

These should be the first drugs to undergo further evaluation in phase 3 studies in order to further evaluate their efficacy and toxicity profiles and optimise dose and administration regimens.

Evaluation required in Phase 2 trials

Carboplatin, etoposide, spartaject, busulfan and nimustine are agents suitable for treatment of PNET and are therefore also suitable for further investigation by the intrathecal route. Topotecan is undergoing intrathecal phase 2 studies in children and adults with refractory neoplastic meningitis; however chemical arachnoiditis has been reported as a dose limiting toxicity. Etoposide and nimustine have already been tested clinically with some encouraging results; however refinement of drug delivery systems may be necessary to prolong exposure in order to overcome their rapid removal from the CSF, their currently observed efficacy may, therefore, be sub-optimal.

Phase 1 studies required

Floxuridine and 4-hydroperoxycyclophosphamide have been tested intrathecally in limited studies and have shown promise in relevant tumour types. The intrathecal use of these two agents should also be further explored.

Pre-clinical evaluation required

Diaziquone is lipophilic and has low ionisation at CSF pH. Together these physical properties suggest it may not remain in the CSF unless delivered in a sustained release formulation or as an infusion. It is active in PNET and leptomeningeal carcinomatosis and has been used intrathecally in human studies. Mercaptopurine has been tested by the intraventricular route in animals and children with leptomeningeal dissemination of ALL but there is no evidence of efficacy in primary brain tumours. Rubitecan has been shown to be safe & effective in a rat model against human glioblastoma multiforme neoplastic meningitis.

Temozolomide is effective in medulloblastoma when given orally. A microcrystalline preparation has been used intrathecally in animal studies justifying further study if an appropriate formulation could be developed. Its lipophilicity would favour a sustained release formulation or an infusion

Pre-clinical animal evaluation

The nine drugs in Table 4 have documented activity in the relevant tumour types but no information was found on intrathecal use. These drugs would be worthy of intrathecal testing.

(Insert Table 4 here - Drugs with documented activity in the relevant tumour types but no information on intrathecal use)

The drugs in Table 5 have been tested in studies in the relevant tumour types by the intrathecal route (some animal, some human) with mixed reports of toxicity and efficacy. With the exception of bleomycin where neurotoxicity seems to be a major problem, these may well be worthy of further research. Carmustine is licensed in a sustained release preparation designed to be implanted into tumour resection cavities as an adjunct to surgery for GBM after relapse. However, it is documented also to have serious neurotoxicity when given systemically and therefore has not been prioritised in the list of drugs for further study.

Gemcitabine has been tested by the intrathecal route in a patient with leptomeningeal carcinomatosis from non small cell lung cancer and has been used intrathecally in non-human primate models [35, 45, 67]. Based upon this, a phase 1 clinical trial of intrathecal gemcitabine has been conducted in ten patients with neoplastic meningitis including one with medulloblastoma. However, dose limiting neurotoxicity was observed in patients who had previously received CNS-directed therapies [15] The authors concluded that the potential for severe neurotoxicity precludes further development of gemcitabine for intrathecal administration.

(Insert Table 5 here - Drugs tested by the intrathecal route (some animal, some human) with mixed reports of toxicity and efficacy)

Discussion

This work helps draw three important conclusions. First, many of the proposed ideal criteria, have not been applicable because of inadequate data in the academic and commercial information domains. A more open shared strategy between pharma and academic researchers of basic pharmacological data is required. Secondly, using supplementary clinical criteria, the systematic review has identified 12 drugs suitable for immediate intrathecal use in medulloblastoma, 15 other candidate drugs were identified for further evaluation prior to human use. Finally, the extended list of agents, identified here as suitable for intrathecal use, justifies further efforts to explore their role as part of brain sparing strategies in clinical trials.

Ideal criteria

The pre-determined criteria were applicable in their entirety in only eight drugs resulting in the current drug selection being based primarily upon alternative criteria including: a) clinical evidence of tumour chemo-sensitivity, b) previously reported intrathecal use and c) reported evidence of neurotoxicity after systemic or intrathecal administration. The overwhelming reason for rejection was because of either insufficient or inconsistent information in the academic domain (Table 2). It remains unclear why this basic physicochemical data is unavailable, highlighting the importance of promoting a more open ethic between pharma and academic groupings exploring novel applications of existing cancer drugs and in particular for intrathecal administration. This large category of known, rejected drugs as well as a presumed larger number of unknown candidate agents in industrial archives constitutes an untapped resource. In contrast, drugs with inconsistent data, but promising early laboratory or clinical evidence of suitability, are a group where further efforts for their evaluation are justified. Furthermore, as new biological agents are developed which affect tumour behaviour via non cytotoxic mechanisms, the lack of publication of physico-chemical criteria or clinical pharmacological data will slow down the process of their selection or rejection for intrathecal use.

Drug selection: From this review, 12 agents were identified as potentially suitable for human use. The three largest previous reviews of this treatment approach do specify optimal drug criteria for intrathecal use but do not specify the method by which they developed their proposed drug selections for intrathecal use.

(Insert Table 6 here - Comparison of candidate intrathecal agents by previous published reviews)

The current review has identified four additional drugs: carboplatin, floxuridine, 4-hydroperoxycyclophosphamide and rubitecan, yet rejected cytarabine (in its standard formulation) and methotrexate because of evidence of neurotoxicity. The extensive experience with these two latter drugs for prophylactic, therapeutic and palliative strategies in acute

leukaemia and lymphoma has permitted comprehensive reporting of neurotoxicity. It has been proposed that enhanced and prolonged drug levels due to reduced permeability of the BBB arising from tumour involvement at sites of CSF efflux is a hypothesis for this observed effect [23, 24, 55, 86]. Carmustine in its wafer preparation (™Gliadel) is used for interstitial therapy for GBM at relapse ***(ref)***. Prior reports of neurotoxicity after intra-arterial administration might have excluded this drug. Its lipophilicity makes it unsuitable as an intrathecal agent without adaptation to its formulation to slow its release or as an infusion. Its current application within a sustained release wafer is, therefore, compatible with the 'ideal criteria' based upon physicochemical properties but not via the intrathecal route aimed at generalised CSF distribution.

Nine drugs were identified with evidence of efficacy against medulloblastoma but insufficient information about their suitability for intrathecal use (Table 4). More information about their physicochemical / cycle specific and neurotoxicity properties is required before they could be accepted/rejected for evaluation by the ideal criteria. The information that was missing was physicochemical (7), cell cycle specificity (4) and neurotoxicity (7). The previous reviews [17, 49, 108] made no suggestions for this category of agents. Drugs, tested by the intrathecal route but with mixed reports of toxicity (n=7 Table 5), were based upon clinical case reports from both animal and human experimentation, limiting the scope of this group as a source of new drugs for testing. There were conflicting reports of neurotoxicity. In only one drug was there a complete physico-chemical dataset (dacarbazine). In three drugs (bleomycin, busulfan and carmustine) drug formulation was reported to influence neurotoxicity and efficacy. This group of drugs highlights the importance of selecting or developing drug formulations that maximise efficacy and minimise neurotoxicity.

Having identified a short list of 12 drugs suitable for human trial via the intrathecal route (table 3) an attempt to select those suitable for immediate use has been made based upon currently available data. Carboplatin, etoposide and nimustine are identified as having the strongest evidence base for intrathecal use. Liposomal cytarabine (Depocyte) and mafosfamide are currently undergoing phase 2 trials; their efficacy and toxicity will need to be judged when given without concomitant chemotherapy or radiotherapy. Mafosfamide is unlicensed and is therefore unavailable for clinical use in trial or therapy (Personal communication: Irene Slavc - irene.slavc@akh-wien.ac.at; Dr Susan Blaney: smblaney@txccc.org). Liposomal cytarabine (Depocyte) is being extensively investigated in adult studies in a variety of cancer types. Preliminary information has identified substantial evidence of neurotoxicity [65, 81]. In selecting any of these drugs for use, the more fat soluble drugs will require either a pharmaceutical formulation aimed at prolonging drug release or the use of intrathecal infusions to sustain drug levels. Such infusional techniques are well developed for intrathecal baclofen aimed at controlling spasticity and could be adapted for such an application [123].

Limitations: Our criteria for accepting or rejecting drugs were applied strictly therefore. Any drug for which we found documentation of it being irritant or neurotoxic was rejected. It is possible that this criteria was applied too strictly since, for example, methotrexate and cytarabine (standard formulation) were excluded and liposomal cytarabine (Depocyte) has been accepted but evidence of neurotoxicity is now emerging. However the objective of the study was to identify drugs with ideal characteristics for intrathecal use.

It is difficult to interpret many studies of intrathecal chemotherapy in terms of efficacy, as in many cases simultaneous systemic chemotherapy or radiation, or both were administered along with intrathecal treatment making it unclear which component of therapy produced the effect. Most patients recruited into such studies are refractory to other treatments and are therefore undergoing such trials as a 'last resort'. Despite this, measurable response to IT therapy, introduced after systemic chemotherapy has proved refractory, is reported as evidence of effect.

Drug administration: The clinical benefits of intrathecal administration need to be balanced against the risks relating to safe prescribing, clinical governance, technical and toxicity issues [38]. Furthermore, in contrast to leukaemia and lymphomas, primary CNS tumours represent anatomical challenges to drug distribution linked to the presence of ventrico peritoneal (VP) shunts, the influence of drainage of the third ventricle to basal cistern by neuroendoscopic third ventriculostomy, distortion of CNS anatomy linked to post-resection tumour bed, post operative incarceration of the posterior fossa and spinal blocks. Finally, the ideal timing of intrathecal administration in relation to debulking surgery is unclear. Such factors will clearly influence the distribution of CSF and any drug it carries. The challenges of drug delivery to the brain have resulted in a considerable volume of research, which may overcome some of these problems, through either local delivery approaches [105, 140] or vascular delivery across the blood brain barrier [57, 79, 103]. However, relatively little research has been focussed upon delivery systems for intrathecal delivery, the main example being that of liposomal cytarabine [22]. The role of efflux inhibitors such as valspodar in combination with intrathecal therapy in order to overcome the problems of removal of drugs from the CSF by multi-drug resistance transporters could also be explored [126].

The application of this method of drug administration in medulloblastoma is timely, as cure rates with combined chemo-radiotherapy for both localised and metastatic cases are improved (>70%, 5 year survival) in school age children. Novel biological markers are identifying patients with favourable tumour types where further de-escalation of neuro-toxic cranial radiotherapy by adjustments to dose/fractionation schedules or fields. The role of systemic

chemotherapy, whilst established in this age group, will be further examined in trials focussing upon minimising toxicity.

In pre-school age children with favourable presentations (non-metastatic, completely resected, desmoplastic histology) survival rates also exceed 70% in recently reported studies [54, 109] using both low and high intensity chemotherapy schedules with or without intrathecal methotrexate and with or without involved field radiotherapy. The interaction between biological markers and these treatment strategies in this age group is yet to be studied [8, 58, 110]. The role of chemotherapy is, therefore, established. The potential for novel biological agents is yet to be explored but is anticipated.

Selecting drugs for IT trial

The most effective and safe way of delivering a drug to the leptomeningeal CSF interface will continue to be a challenge. In seeking to optimise drug delivery, drug selection is the first step. The route and method of administration will need to be studied further i.e. the intraventricular route, the lumbar route, by bolus and by infusion. Anatomical factors will require consideration including the effects of tumour location, CSF circulation, including VP shunting and post operative complications affecting the tumour bed. Once drugs have been tested in phase 1 studies, then phase 2 studies looking for efficacy in patients with either newly presenting or relapsed leptomeningeal disease will be necessary. Once a drug has been assessed as effective by intermittent or infusional techniques of IT administration, then phase 3 trials to evaluate its clinical effectiveness or preparation of sustained release formulation for intermittent IT administration would be justified. The preparatory clinical testing can only be developed within centres with the relevant neuroscience / pharmaceutical / pharmacological research expertise.

Conclusion

This review has extended the list of candidate agents suitable for further investigation of intrathecal treatment of leptomeningeal medulloblastoma. It has identified the importance of making basic physico-chemical criteria available to the academic domain by pharma and academic research groupings in order to accelerate the development of new cancer agents. It has highlighted the opportunity to replicate the success of CNS targeting of drug therapy in leukaemia and lymphoma, by proposing trials of novel intrathecal chemotherapy in medulloblastoma. It has identified the need to establish an acceptable process for selecting new drugs for trial and a suitable trial design.

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Table 1: Summary of ideal clinical, biological and physicochemical / pharmaceutical properties used to justify selection or rejection of drugs.

Property Required
ClinicalNon-irritant Neurotoxicity low or absent Evidence of tumour sensitivity
Biological CSF transport system absent Cell cycle non-specific agent
Physicochemical & pharmaceutical Active in CSF Hydrophilic and/or ionised at CSF pH therefore low membrane permeability (to minimise diffusion out of CSF) Molecular Size (›700 Da) Suitable formulation readily available

Table 2: List of chemotherapy drugs considered with selection / rejection status and rejection justification

Table 2a - Rejected chemotherapy agents plus justification

Irritant	***No tumour activity***	***No information***	***Requires activation***	***Neurotoxic***	***Neurotoxic and irritant***	***Neurotoxic via IT route***
Aclarubicin	Carbetimer	AG-337 (Noltatrexed)	Capecitabine	Acivicin	Altretamine	Doxorubicin
Amsacrine	Mitoguazone	Amonafide	Cyclophosphamide	Asparaginase	Chlorambucil	Melphalan
Azathioprine		Amrubicin	Mitomycin	Carmofur		Mitozantrone
Dactinomycin		Azacitidine	Procarbazine	Cisplatin		**Fluorouracil
Daunorubicin		Bendamustine	Trofosfamide	Cladribine		
Epirubicin		Bisantrene	*Thiotepa	Docetaxel		
Idarubicin		Caracemide		Doxifluridine		
Mustine (Mechlorethamine)		Carboquone		Fludarabine		
Paclitaxel		Chlorozotocin (DCNU)		Fotemustine		
Pirarubicin		Chromomycin		Gemcitabine		
Piroxantrone		Clofarabine		Hydroxyurea		
Plicamycin		Crisnatol		Ifosfamide		
Streptozocin		Decitabine		Methotrexate		
Valrubicin		Echinomycin		Mitotane		
Zorubicin		Edatrexate		Oxaliplatin		
		Enloplatin		Pentostatin		
		Enocitabine		Sparfosic acid		
		Estramustine		Spiromustine		
		Homoharringtonine		Suramin		
		Ilmofosine		Tegafur		
		Improsulfan		Vinblastine		
		JM-216 (Satraplatin)		Vincristine		
		Lobaplatin		Vindesine		
		Miboplatin		Vinorelbine		
		Mitobronitol				

		Mitozolamide				
		Nedaplatin				
		Pemetrexed				
		Peplomycin				
		Pipobroman				
		Piritrexim				
		Porfiromycin				
		Prednimustine				
		Raltitrexed				
		Ranpirnase				
		Razoxane				
		Sebriplatin				
		Semustine				
		Sobuzoxane				
		Teloxantrone				
		Thioguanine				
		Tirapazamine				
		Treosulfan				
		Trimetrexate				
		Ubenimex				

* Systemic administration delivers concentration to IT route
** Also irritant

Table 2b – Selected drugs

1. Carboplatin	Selection	Table 3
2. Cytarabine	Selection	Table 3
3. Diaziquone	Selection	Table 3
4. Etoposide	Selection	Table 3
5. Floxuridine (FdUrd)	Selection	Table 3
6. 4-hydroperoxycyclophosphamide	Selection	Table 3
7. Mafosfamide	Selection	Table 3
8. Mercaptopurine	Selection	Table 3
9. Nimustine (ACNU)	Selection	Table 3
10. Temozolomide	Selection	Table 3
11. Topotecan	Selection	Table 3
12. Eflornithine	Selection	Table 4
13. Mitolactol (Dibromodulcitol)	Selection	Table 4
14. Didemnin B	Selection	Table 4
15. Irinotecan	Selection	Table 4
16. Lomustine (CCNU)	Selection	Table 4
17. Lonidamine	Selection	Table 4
18. Menogaril	Selection	Table 4
19. Tauromustine	Selection	Table 4
20. Teniposide	Selection	Table 4
21. Bleomycin	Rejection	Table 5 – neurotoxic when given IT
22. Busulphan	Selection	Table 5
23. Carmustine (BCNU)	Selection	Table 5
24. Dacarbazine	Selection	Table 5
25. Fazarabine	Selection	Table 5
26. Ranimustine (MCNU)	Selection	Table 5
27. Zinostatin	Selection	Table 5

Table 3: Drugs graded by eligibility for trial by intrathecal administration for medulloblastoma

Legend

OWPC = octanol/water partition coefficient >0 = lipophilic; <0 = hydrophilic (different values obtained from different references)

pKa = dissociation constant. pKa <5.3 or >9.3 indicate an ionisation of >99% at CSF pH of 7.3
MW = molecular weightIV = intraventricular. IL = intralumbar. IC = intracavity/tumour. IT = intrathecal

RMM - refractory meningeal malignancy, MB = medulloblastoma, LMC = leptomeningeal carcinomatosis, LMM = leptopmeningeal meningitis, NM = neoplastic meningitis***3a***

Agents under trial.

DRUG	***OWPC***	***pKa***	***MW***	***Evidence of medulloblastoma (MB / PNET) chemosensitivity***	***Evidence of IT use.***	***Cell cycle phase specificity***	***Comments***	***Refs***
Cytarabine (liposomal formulation)	-2.46	4.3	243	Evidence of MB sensitivity, Randomised Clinical Trial in NM had 13/18 responders with IT liposomal v 3/17 with free cytarabine.	Licensed in lymphomatous meningitis in adults. Phase 1 trial in children with NM established maximum tolerated dose and showed benefit in 8/14 pts. Phase 2 trial is in development.	S phase	Neurotoxic in standard formulation. Liposomal preparation used for IT is less toxic and half life in CSF is prolonged up to 40 times, though is less in children than adults. Dexametasone is required to avoid arachnoiditis.	[1, 11, 20, 27, 32, 33, 36, 37, 42, 44, 64, 66, 68-70, 73, 77, 78, 87, 95, 96, 130, 142]
Mafosfamide	0.56,-2.11		401	MB, PNET, ependymoma pts, LMC -rabbit only	IV -non-human primate, IV –rabbit. Phase 1 study in patients with RMM, IV+ IL paediatric patients showed good effect + minimal toxicity. Phase 1 study has determined maximum tolerated dose in children <3yrs with newly diagnosed embryonal tumours – phase 2 trial in progress	non	Cyclophosphamide derivative, undergoes spontaneous hydrolysis to active species	[1, 17, 21, 42, 87, 95, 96, 104, 120, 121, 128]

Table 3b: Agents suitable for clinical trial.

DRUG	***OWPC***	***pKa***	***MW***	***Evidence of medulloblastoma (MB / PNET) chemosensitivity***	***Evidence of IT use.***	***Cell cycle phase specificity***	***Comments***	***Refs***
Carboplatin	-0.46		371	High grade gliomas, MB, PNET, ependymoblastoma	IT in rats showed this to be the least neurotoxic of the platins. Neurotoxicity not seen until lethal dose	non		[39, 41, 95, 96, 100, 107, 118, 127]
Etoposide	0.6	9.7	589	MB	IV -dogs, humans IV - metastatic MB, malignant meningitis. Used IV in paediatric patients with good effect + minimal toxicity	Late S, G2	Poor CSF distribution following IV administration, possibly due to rapid CSF clearance due to lipophilicity and/or efflux by P-glycoprotein and MDR-associated protein 1. Possible problem with IL route due to concerns of drug and preservatives causing spinal cord damage.	[1, 40, 42, 87, 95, 96, 112, 114, 121, 126, 128, 133]
Nimustine (ACNU)	0.39 Water + lipid soluble		309	Pilocytic astrocytoma, meningeal spread of MB, PNET, glioblastoma, anaplastic glioma.	MC - rat, dog, IV in meningeal spread of MB, PNET, glioblastoma, anaplastic glioma, A phase1/11 study involving IV/IL/ IT admin in 21 patients (including children) with refractory disseminated MB showed efficacy in some patients	non	When given IV, needed infusion - bolus did not give adequate subarachnoid spread as CSF half-life very short(approximately27min) High priority for future study in appropriate delivery system	[6, 42, 61, 63, 74-76, 83, 87, 95, 96, 98, 129, 131, 132, 146-149]

Table 3c: Drugs requiring further investigation before clinical trial.

DRUG	***OWPC***	***pKa***	***MW***	***Evidence of medulloblastoma (MB / PNET) chemosensitivity***	***Evidence of IT use.***	***Cell cycle phase specificity***	***Comments***	***Refs***
Floxuridine (FdUrd)	-1.16	7.44	246	MB, glioma LMC -animal + humans, NM	LMC, NM by continuous IT infusion. Intracavitary administration may be useful in small volume malignant brain tumours			[1, 42, 87, 91-96, 144]
4-hydroperoxy-cyclophosphamide			293	Promising phase 1 trial IT in MB, PNET	Promising phase 1 trial IT in MB, PNET. IV administration in monkeys	non		[7, 52, 95, 96]

3d: Drugs requiring further investigation, lower priority.

DRUG	***OWPC***	***pKa***	***MW***	***Evidence of medulloblastoma (MB / PNET) chemosensitivity***	***Evidence of IT use.***	***Cell cycle phase specificity***	***Comments***	***Refs***
Diaziquone	-0.758	low ionisation at physiological pH	364	9L rat brain tumour, LMC, GBM, AA, paed brain tumours, RMM, recurrent glioma – phase 11 studies, MB xenograft in mice	Rat, IV-non-human primate studies, Human patients including children with RMM – phase 1/11 studies – good response		Low aqueous solubility has caused formulation problems. Drug shows high rate of clearance from CSF	[1, 13, 14, 21, 31, 42, 43, 47, 62, 71, 78, 87, 95, 96, 115, 127, 150]
Mercaptopurine	0.01	7.77, 11.17	170	LMD of ALL	IV - monkey then children	S - phase	Cleared from CSF at 0.63ml/min (bulk flow 0.4ml/min) suggesting an additional mechanism of elimination - possibly efflux by MDR-associated protein 1 and monocarboxylic acid transporters	(25, 59, 60, 91, 105, 107)
Rubitecan			393	safe & effective in rat model against human GBM xenograft NM	IT safe & effective in rat model of GBM NM	S-phase		
Topotecan	0.83, -0.3	6.35, 10.1	458	ependymoma, MB, high grade glioma xenografts	IV non-human primate. IV & IL to children & adults with refractory neoplastic meningitis. Phase 2 study underway.	S-phase	Chemical arachnoiditis dose limiting toxicity. Rapid elimination from CSF. Novel mechanism of action	[1, 10, 18-21, 87, 95, 96, 99, 122, 137]

Table 3e: Drug with insufficient information to grade

DRUG	***OWPC***	***pKa***	***MW***	***Evidence of medulloblastoma (MB / PNET) chemosensitivity***	***Evidence of IT use.***	***Cell cycle phase specificity***	***Comments***	***Refs***
Temozolomide	-0.58, -1.32		194	CNS tumour xenografts, NM Phase 2 studies in MB, astrocytoma, glioma, GBM	microcrystalline prep with increased solubility - used IT in rats with NM + malig glioma sub arachnoid xenografts		Spontaneous conversion to active mitomycin in physiological conditions. Highly insoluble in aqueous solution, microcrystalline form increased solubility	[1, 42, 50, 87, 95-97, 111, 124]

Table 4: Drugs with documented activity in the relevant tumour types but no information on intrathecal use.

DRUG	OWPC	pKa	MW	Evidence of tumour sensitivity	Previous IT use.	Cell cycle phase specific	Neuro-toxicity	Comments	Refs
Didemnin B	3.173		1112	Some response seen in GBM and progressive high grade gliomas				Natural marine product, antiviral and antineoplastic activity	[95, 96, 127]
Eflornithine	-2.945		182	In combination with mitoguazone, response seen in anaplastic astrocytoma and GBM					[95, 96, 127]
Irinotecan	0.03 (pH 1-6) 0.095 (pH9-12). At pH7-slightly more lipophilic but likely to be more hydrophilic than lipophilic	1.07, 7.89	677	peripheral PNET, neuroblastoma xenografts, MB, glioma, ependymoma xenografts. GBM, ependymoma, MB (animal models), some evidence of activity in recurrent glioma		S-phase		Requires metabolism by carboxylesterase in liver & tissues to SN-38 to provide most of it's cytotoxic activity – it is not known if this would occur in the CSF	[28, 59, 87, 95, 96, 106, 135, 138]
Lomustine (CCNU)	2.629		234	MB, glioma		non		Alkylating and carbamoylating agent	[10, 42, 62, 85, 87, 95, 96, 114, 141]
Lonidamine	4.407		321	Prolongation of survival + rate of 1 year survivors (62 v 35%) supratentorial glioma			Drowsiness, weakness	Inhibits lactate production causing interference with energy metabolism of cancer cells	[87, 95, 96, 127]
Menogaril	1.066		542	High grade glioma, phase 1 and 11 trials give conflicting results		? non		Anthracycline, therefore likely to be irritant	[42, 87, 95, 96, 127]
Mitolactol (Dibromodulcitol)	-0.426		308	MB, PNET, ependymoma - single agent, moderate effect				long duration of presence in CSF with a half life of around 24 hours	[39, 42, 84, 87, 95, 96, 101, 116, 117]
Teniposide	-0.03(estimated by calculation with low confidence probably higher)	10.13	657	MB in cell culture			As etoposide	efflux by P-glycoprotein	[39, 42, 87, 89, 95, 96, 128, 134]
Tauromustine	-0.299		287	AA, glioblastoma, clinical improvement seen in 19/46 patients		? non			(59, 60, 71)

Table 5: Drugs tested by the intrathecal route (some animal, some human) with mixed reports of toxicity and efficacy:

DRUG	***OWPC***	***pKa***	***MW***	***Evidence of tumour sensitivity***	***Previous IT use IV = intra-***	***Cell cycle phase specific***	***Neurotoxicity***	***Comments***	***Refs***
Bleomycin	-2.57		1416	Intracerebral administration in rat 9L gliosarcoma. Administered safely in liposomes in human cerebral glioma. Given IC in GBM - safe but efficacy doubtful. <25% increase in survival in LMC rat model	phase 1 study IC - no toxicity. Rat, beagle, human (phase 1 IV), depot preparation	Cycling & non-cycling cells M & G2 phases most sensitive	Vascular necrosis after IT (beagle), death after IC administration in craniopharyngioma patient	Antibiotic - binds to DNA - strand scission	[25, 42, 78, 82, 88, 90, 95, 96, 113]
Busulphan	-0.52		246	MB/Glioma/ependymoma - mice. Glioblastoma - rat. MB-mice	Rat	Non	Confusion + seizures - high dose.	Irritant. Bifunctional alkylating agent. Poorly water soluble however water-soluble microcrystalline formulation (Spartaject) been developed. Given IT in rats, non-human primates, adults with LM disease + phase 1 trial in children with LMD from brain tumours	[3, 5, 26, 42, 51, 56, 87, 95, 96, 122, 130]

Carmustine (BCNU)	1.53		214	Intravenous preparation licensed in brainstem glioma, MB, astrocytoma, ependyoma, and metastatic brain tumours. GLIADEL Implant licensed in high-grade malignant glioma and GBM.	IT - in hybrid liposomes - rat + dog	Non	Convulsions, cerebral oedema in patients with implants. No Adverse Drug Reactions, non-toxic in rat/dog in liposomes. Acute encephalopathy after intracarotid administration, encephalomyelopathy - coma + death with high dose, neuroretinitis	Alkylating and carbamoylating agent. DNA alkylation followed by protein carbomoylation. Causes local venous irritation	[2, 9, 29, 42, 46, 48, 64, 71, 72, 85, 87, 95, 96, 128, 130, 136, 143]
Dacarbazine	-0.24	4.42	182	Melanoma - including primary CNS	Rat. 3 case reports human patients	Non	Very toxic in rat. CNS reaction in one patient case report	Requires demethylation for activation, though dacarbazine itself shows cytotoxic activity. Irritant-extravasation causes tissue damage + severe pain	[9, 12, 34, 42, 78, 85, 87, 95-97, 145]
Fazarabine			496	Lack of activity in phase 2 trial high grade glioma. Solid tumour activity + leukaemia xenografts. Potentially useful for NM from a variety of tumours	IT + IV (Ommaya reservoir) in Rhesus monkeys	Probably s-phase	Transient changes in CSF profiles but no evidence of neurotoxicity after IV in monkey	Cytarabine analogue. Inhibits DNA synthesis + methylation. Nucleoside metabolite, intracellular activation needed by deoxycitidine kinase. Clearance from CSF five times higher than CSF bulk flow rate in monkey	[60, 95, 96, 119]
Ranimustine (MCNU)	-1.29		328	pilocytic astrocytoma	Longer half life than ACNU in dogs. IT admin in 21 patients (including children) with refractory disseminated MB showed efficacy in	Non	Mild histological changes in dog brain after IV admin. IC admin caused marked brain oedema + focal necrosis. Paraplegia + double incontinence in some patients receiving multiple	Nitrosourea	[42, 74, 87, 95, 96, 98, 146, 149]

					some.		IL bolus injections		
Zinostatin				Glioblastoma, astrocytoma	single case report		No CNS toxicity when given via carotid artery	Antineoplastic antibiotic. Does not permeate BBB in normal brain. Half life CSF=50sec	[74, 87, 95, 96, 98, 146]

Table 6: Comparison of candidate intrathecal agents by previous published reviews

Fleischack [49].	Ruggiero [108].	Blaney [17]	Conroy
Intracavitary bleomycin			
			Carboplatin
Cytarabine	Cytarabine		
Liposomal cytarabine (DepoCyte™)	Liposomal cytarabine (DepoCyte™)	Liposomal cytarabine (DepoCyte™)	Liposomal cytarabine (DepoCyte™)
Diaziquone			Diaziquone
Etoposide			Etoposide
			Floxuridine (FdUrd)
			4-Hydroxyperoxy-cyclophosphamide
Mafosfamide	Mafosfamide	Mafosfamide	Mafosfamide
Mercaptopurine	Mercaptopurine		Mercaptopurine
Methotrexate	Methotrexate		
	Monoclonal antibodies		
Nimustine (ACNU)			Nimustine (ACNU)
			Rubitecan
	Temozolomide		Temozolomide
	Thiotepa		
Topotecan		Topotecan	Topotecan