The use of Ommaya reservoirs to deliver central nervous system directed chemotherapy in childhood acute lymphoblastic leukaemia.

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Abstract:

Prophylactic eradication of central nervous system (CNS) leukaemia is the current standard of care in treating childhood acute lymphoblastic leukaemia (ALL). This is conventionally achieved through regular lumbar punctures with intrathecal injections of methotrexate into the cerebrospinal fluid (CSF). Ommaya reservoirs are subcutaneous implantable devices that provide a secure route of drug delivery into the CSF via an intraventricular catheter. They are an important alternative in cases where intrathecal injection via lumbar puncture is difficult. Among UK Paediatric Principal Treatment centres for ALL we found considerable variation in methotrexate dosing when using an Ommaya reservoir. We review the current safety and theoretical considerations when using Ommaya reservoirs and evidence for methotrexate dose adjustments via this route. We conclude by summarising the pragmatic consensus decision to use 50% of the conventional intrathecal dose of methotrexate when it is administered via Ommaya reservoir in front-line ALL therapy.

Key points:

1. Ommaya reservoirs can be used to deliver chemotherapy to the central nervous system via an implanted intraventricular catheter.
2. A survey of UK Paediatric Principal Treatment centres revealed a wide range of dosing of chemotherapy agents when converting from intrathecal to intraventricular (Ommaya) delivery.
3. Review of the literature supports reduced dosing when CNS-directed therapy is given by Ommaya reservoir in place of conventional intrathecal therapy.

1. Introduction:

The central nervous system (CNS) remains an important sanctuary site for childhood acute lymphoblastic leukaemia (ALL). [1]. Although overt CNS infiltration is only seen in 2-5% of children at initial diagnosis, approximately 40% of relapses involve the CNS [2, 3]. Without CNS-directed chemotherapy up to 75% of patients will relapse within the CNS [4], and yet no reliable predictors of relapse-risk have been identified. Both clinical observations and experimental models suggest that subclinical CNS infiltration is likely to be present in the majority of patients at initial diagnosis. For this reason, all patients currently receive "prophylactic" CNS treatment regardless of the presence of detectable leukaemia in samples of cerebrospinal fluid (CSF). This treatment is potentially toxic to the developing brain and can

produce neurocognitive impairment [5]. In addition, relapse within the CNS can be refractory to conventional chemotherapy and/or bone marrow (BM) transplantation [1]. CNS control is now often achieved using intrathecal chemotherapy (delivered directly into the circulating CSF via lumbar puncture) [4, 6]) and systemic drugs with good CNS penetration, instead of cranial irradiation. This change followed observation of the long-term adverse effects of cranial irradiation, such as development of secondary cancers, endocrinopathies and neurocognitive impairment [1]. Methotrexate is the commonest intrathecal agent used in ALL, either alone or in combination with cytarabine and hydrocortisone (so called triple therapy). Several studies have demonstrated comparable efficacy and similar rates of CNS relapse using intrathecal methotrexate or triple therapy, compared with results using cranio-spinal irradiation [7-9]. Consequently, many trial groups now use intensive intrathecal chemotherapy as the standard of care for prophylaxis and treatment of CNS leukaemia, whilst others reserve cranial irradiation for those at highest risk of CNS relapse.

Clinically, there are two methods of delivering CNS-directed chemotherapy. Conventionally, intrathecal lumbar puncture is used to administer chemotherapy into the lumbosacral CSF space. Alternatively, chemotherapy can be administered via an implantable Ommaya reservoir, a small device comprising a capsule, situated between the cranium and overlying skin connected to a catheter communicating directly with one of the lateral ventricles [10]. The Ommaya reservoir allows for repeated CSF sampling and for chemotherapy to be delivered directly into the cerebral ventricles, rather than relying on CSF flow from the lumbar to the cranial regions. While lumbar punctures are the standard route of delivery for intrathecal chemotherapy, Ommaya reservoirs remain an important alternative for CNS access. Examples of situations where an Ommaya reservoir might be used include; patients where spinal anatomy or obesity make lumbar punctures technically challenging, and patients with hydrocephalus, microcephaly or known abnormalities of CSF flow [11]. In addition, for some patients with refractory CNS relapse use of an Ommaya facilitates frequent reliable delivery of adequate doses of CNS-therapy without the need for repeated general anaesthesia.

Although the intrathecal dose of methotrexate is well established and standardised, there is a lack of definitive evidence regarding the optimal dosing of chemotherapy when given as an intraventricular injection via an Ommaya reservoir. We surveyed all UK Paediatric Principal Treatment Centres and found considerable variation in the dose of intraventricular chemotherapy administered to children with ALL, ranging from 100% dosing (i.e. identical to

the calculated intrathecal dose) to 20% dosing (figure 1). There is a clinical need for guidance in this area, as methotrexate-induced neurotoxicity remains a significant side effect of CNS-directed therapy, whilst under-dosing of methotrexate may increase CNS relapse. In this article, we review important safety and efficacy considerations for methotrexate administered via Ommaya reservoir and discuss the clinical and pharmacological differences between intrathecal and intraventricular administration in children with ALL. We conclude by summarising a consensus decision for future dosing of intraventricular methotrexate in ALL.

2. Clinical advantages and limitations of the Ommaya reservoir:

The advantages and limitations of Ommaya reservoirs are discussed below (summarised in table 1).

2.1 Safety:

Most published studies and case series using Ommaya reservoirs for intraventricular chemotherapy in meningeal leukaemia are now more than 30 years old. Studies reporting on Ommaya reservoirs in ALL are very rare in contemporary literature. Furthermore, a randomised controlled trial (RCT) comparing intraventricular chemotherapy with intrathecal chemotherapy in ALL has never been performed. It appears that use of Ommaya reservoirs for CNS leukaemia declined during the 1980s, probably due to safety concerns relating to relatively common CNS infections and neurological complications associated with their early use. In modern treatment regimens, Ommaya reservoirs are generally reserved for patients with difficult access to the lumbar spine, or in those with abnormal CNS anatomy, such as hydrocephalus, microcephaly or known abnormal CSF flow [11]. It is therefore challenging to define precisely the safety of Ommaya reservoirs in unselected children with leukaemia. However, Ommaya reservoirs are also used in treatment of paediatric brain tumours. While direct comparison between these two patient populations should be approached with caution, recent case series provide useful data on contemporary short-term complication rates.

2.2 Bacterial infection:

Peyrl and colleagues describe in detail their meticulous aseptic approach to administering intraventricular chemotherapy to children with CNS tumours via Ommaya reservoir [12]. Their approach resulted in just one child out of 98 developing an Ommaya-related CNS infection over 20 years. In addition to strict adherence to aseptic technique when delivering intraventricular chemotherapy, they also administered prophylactic antibiotics prior to surgical incision and for 3-5 days post-operatively. Modern neurosurgical technologies were

employed to aid catheter placement and MRI studies of the brain and spinal cord were conducted prior to insertion, and the position of the catheter tip was confirmed on CT or MRI scan, post-operatively. This group also avoided using the reservoir for 5 days post-operatively to reduce the risk of retrograde flow of intraventricular therapies through the catheter tract and to promote wound healing around the reservoir. This approach resulted in very low rates of Ommaya-related CNS infection in a large cohort of paediatric cancer patients. It should be noted that this was a case series rather than a comparative study so the contribution of each individual component to the low infection rates is unknown. Another large retrospective analysis of 616 adult and paediatric cancer patients with Ommaya reservoirs report infection rates of 5.5% [13]. Taken together, these reports demonstrate a considerable reduction in the incidence of bacterial infections associated with Ommaya reservoirs, compared with earlier reports, which ranged between 15-41% [14-16]. Importantly, the studies agree that increasing numbers of intra-Ommaya injections correlate with an increased risk of infection. However, Peyrl and colleagues virtually eliminated this risk with a rigorous aseptic protocol for device access [12].

2.3 Misplaced Ommaya catheters:

In older studies, Ommaya catheters were occasionally displaced into the brain parenchyma, often leading to severe complications, such as focal leukoencephalopathy [17-19]. Modern neurosurgery by comparison benefits from significant improvements in intraoperative neurosurgical technologies and perioperative neuroimaging [20-22]. These advances should considerably reduce the risk of Ommaya-catheter malposition and allow for accurate assessment of catheter-tip position prior to chemotherapy administration. These improvements optimise safe Ommaya reservoir placement and are likely to reduce significantly the adverse effects of using these implantable devices for administering CNS-directed chemotherapy.

2.4 Neurotoxicity:

Methotrexate-induced neurotoxicity has been extensively reported in children treated for ALL. It has a variety of clinical presentations from an acute encephalopathy, seizures or a stroke-like syndrome to chronic neurocognitive deficits. Stroke-like syndrome is seen in 1-4% of children treated in modern protocols [23-25] and presents 2 to 14 days post-exposure to methotrexate with fluctuating focal neurological signs, such as; encephalopathy, seizures, expressive dysphasia, and hemiparesis [24-27]. MRI studies of symptomatic children typically demonstrate patchy leukoencephalopathy. Interestingly, MRI studies in asymptomatic children

receiving methotrexate as CNS-prophylaxis demonstrate radiological leukoencephalopathy in 21-27% of cases, suggesting high rates of subclinical white matter damage [24, 26]. One study indicated that children with subclinical leukoencephalopathy are more likely to have long-term neurobehavioral deficits than patients on identical treatment protocols without MRI evidence of leukoencephalopathy [26]. Additional studies have investigated neurocognitive functioning in children treated with contemporary chemotherapy-only treatment regimens [5]. Some studies observe that while most children generally have age-appropriate neurocognition, those treated with higher-intensity protocols are at greater risk of long-term deficits in neurocognitive functioning [28, 29] and executive function [30]. Another large follow-up study supports these observations in a cohort of long-term survivors but did not identify an association with treatment intensity [31]. The relationship between methotrexate drug levels and neurotoxicity is complex. There is evidence that the intensity of methotrexate exposure is associated with neurotoxicity [32] and one study found an association between individual methotrexate exposure levels (area under the curve) and leukoencephalopathy on MRI scanning [24]. On the other hand, there is no clear dose response, patients with stroke-like syndrome can usually be re-exposed to the same dose without recurrence, and it is likely that additional risk factors are present [33].

There is no evidence that intraventricular methotrexate produces higher rates of neurotoxicity than intrathecal methotrexate, although this has not been formally tested in randomised trials. However, the known higher methotrexate concentration in the ventricular CSF when identical doses are given intrathecally or via the intraventricular route (discussed in detail below) raises a theoretical concern of enhanced neurotoxicity and supports the need to consider dose reduction via the intraventricular route.

2.5 Systemic side effects with intraventricular chemotherapy:

Owing to slow diffusion of methotrexate across the blood-brain barrier, CSF can act as a reservoir for systemic drug perfusion, whereby low concentrations of methotrexate continuously enter the circulation from the CSF [34-36]. Indeed, systemic exposure as measured by red cell accumulation of methotrexate appears greater with IT MTX than the same dose given orally [37] and timing of intrathecal MTX can influence systemic ALL responses as measured by day 8 peripheral blast count [38]. Furthermore, long exposure to subtherapeutic levels of methotrexate can cause myelosuppression. Leucovorin is sometimes used to alleviate

myelosuppression without apparent compromise of methotrexate efficacy [39]. Again, theoretically the high concentrations of methotrexate achieved using Ommaya reservoirs may potentiate these systemic effects if no corresponding dose reduction is used.

2.6 Clinical advantages of Ommaya reservoir:

Ommaya reservoirs are a very efficient method of accessing the CNS, compared with repeated lumbar punctures. Following neurosurgical placement, the procedure of sampling CSF and then administering chemotherapy is straightforward and relatively painless [12, 14]. Furthermore, while training in aseptic use is of paramount importance, accessing the Ommaya reservoir is technically simple and does not require general anaesthesia. Some children with abnormal spinal anatomy present a recurrent challenge and an emerging clinical indication for Ommaya reservoirs is the increasing prevalence of obese and severely obese children [40, 41], which makes repeated lumbar CSF access difficult. With a meticulous aseptic approach, Ommaya reservoirs provide a safe, effective alternative to repeated lumbar puncture. Interestingly in one small study it was reported that patients receiving alternating intrathecal and intraventricular chemotherapy overwhelmingly preferred the Ommaya route [42].

3. Efficacy of intraventricular methotrexate versus intrathecal methotrexate in treating ALL:

No published RCTs have compared the two routes. However, two small studies indicate possible superior efficacy of intraventricular methotrexate for treatment of CNS ALL. Bleyer and colleagues published the first study in 1979 which included 10 children who developed CNS relapse despite monthly intrathecal methotrexate maintenance treatment [43]. The children were re-induced and remission maintained using intraventricular methotrexate via an Ommaya reservoir. Seven of the eight evaluable children had significantly longer remissions using intraventricular methotrexate, compared with intrathecal methotrexate. The median CNS remission duration with intraventricular methotrexate was 475 days, compared with 286 days during prior treatment with intrathecal methotrexate ($p<0.05$). Equivalent doses of methotrexate were used for both routes of administration (12-15mg/m^2, max dose 18mg), unless participants had previous methotrexate-related neurotoxicity, in which case the dose was reduced (averaging 8mg/m^2). There was one infection in the Ommaya reservoir group; a *Staphylococcus epidermidis* meningitis which was successfully treated with intraventricular

and intravenous methicillin and which allowed the device to remain functional 4 years later. The authors concluded that, in their experience, intraventricular methotrexate is an efficacious therapy if conducted under expert neurosurgical care and with meticulous aseptic technique.

In 1995, a second retrospective study of 21 adult ALL patients receiving either intraventricular (n=9) or intrathecal (n=12) methotrexate for meningeal leukaemia also demonstrated a considerable improvement in CNS leukaemia with intraventricular methotrexate [44]. In patients receiving intraventricular methotrexate, 89% (8/9) had a complete response (CR), defined as complete clinical remission and an absence of malignant cells in CSF from two consecutive weekly CSF samples. None of these eight patients had further CNS relapse and three had no further events, with a median follow-up of 5 years. By comparison, 33% (4/12) of patients receiving intrathecal methotrexate achieved CR, yet two of them developed systemic and CNS relapse. The median survival time after intraventricular treatment was 152 weeks, compared with 14 weeks for intrathecal therapy (p=0.003). All patients receiving intraventricular methotrexate responded to treatment; the single patient who did not have a CR had a partial response (defined as a 50% reduction in CSF malignant cells with only transient remission). In comparison, 7/12 patients receiving intrathecal methotrexate failed to achieve even a partial response to treatment, which greatly affected cohort median survival times.

It is difficult to draw definitive conclusions from so few comparative studies and small patient numbers. However, given intraventricular methotrexate has been shown to be more effective than intrathecal methotrexate in treating overt meningeal ALL, a multi-centre randomized control trial might be warranted to compare the safety and efficacy of intraventricular versus intrathecal methotrexate for relapsed/refractory CNS leukaemia.

4. Optimal dosing of methotrexate using Ommaya reservoirs:

Methotrexate is the cornerstone of CNS-directed therapy in childhood ALL. It inhibits dihydrofolate reductase, thereby limiting the availability of reduced folates for purine and pyrimidine synthesis, essential for replication [45]. It is important to consider optimal concentrations of methotrexate to ensure complete ALL clearance from the CNS, while preventing detrimental side effects that can result from overexposure. Based on *ex vivo* studies using human ALL cells, prolonged exposure to methotrexate concentrations >1 μmol/L is more important than brief periods of very high methotrexate levels for eradication of leukaemic cells

[46]. An emphasis on prolonged leukaemic exposure to methotrexate to optimise cytotoxicity is supported by an abundance of pre-clinical work, which is discussed in detail by Ettinger and colleagues [47]. The optimal exposure time is thought to be 48-72 hours as the cell cycle takes approximately 3 days [48, 49], however, it might be longer in the CNS due to slower proliferation kinetics in this microenvironment [50, 51].

CSF is formed in the choroid plexus of the cerebral ventricles. It flows through the subarachnoid space in the spinal column and is reabsorbed into plasma, mostly via the arachnoid villi [52]. Several studies have reiterated the observation made by Bleyer et al in 1973, that active meningeal leukaemia appears to increase methotrexate half-life within CSF [53-55]. Grossman and colleagues demonstrated that neoplastic infiltration of the meninges results in abnormal CSF flow dynamics, such as ventricular outlet obstructions, spinal canal abnormalities and cortical flow delays [56]. Delayed ventricular drainage of methotrexate may sustain high concentrations within the ventricles, potentially leading to neurotoxicity. In one report, children with overt CNS disease (ALL or non-Hodgkin's lymphoma) had significantly higher CSF methotrexate concentrations compared with children treated prophylactically, independent of patient age [54]. A similar study observed normal CSF flow in patients with CNS remission [57], suggesting that CSF dynamics are crucially affected by the site and extent of meningeal disease. Despite this body of evidence, the clinical implications of these observations and how they might impact on rational dosing of CNS-directed therapy are unclear and modern ALL protocols do not adjust intrathecal doses based on CNS leukemic load.

There has never been a randomised trial of Ommaya vs lumbar puncture delivery of methotrexate. Most studies comparing the two routes were conducted in the 1970s and 1980s and are mainly small case series. Despite this, some consistent and important observations emerge that help inform decision making on dosing, as detailed below:

1. *Delivery of methotrexate via an Ommaya reservoir results in higher and more consistent levels of methotrexate in the cerebral ventricles than delivery via lumbar puncture*

In 1975, Shapiro and colleagues directly compared Ommaya (intraventricular) and lumbar puncture (intrathecal) administration of methotrexate and showed that intraventricular delivery provided more consistent CSF concentrations when compared to lumbar injection [35]. They administered methotrexate with ^{131}I-labelled albumin and subsequently scanned patients at 1-, 16- and 40-hours post-administration to determine perfusion via the two routes. Methotrexate

via Ommaya reservoir was delivered at a dose of 6.25mg/m^2, while 6.25mg/m^2 and 12.5mg/m^2 doses were compared when given intrathecally via lumbar puncture. From this analysis, they observed that despite good CSF flow and manometrics at the time of lumbar puncture, lumbar puncture injections were often misplaced and methotrexate failed to enter the CSF. They further observed that even when lumbar puncture was successful, there was considerable interpatient variability in methotrexate perfusion within the CSF, with up to 100-fold variations in intraventricular concentration when administered via intrathecal lumbar injection. Furthermore, the larger lumbar dose of 12.5mg/m^2 did not correlate with a higher ventricular concentration of methotrexate. By comparison, ventricular and lumbar CSF methotrexate concentrations were noted to be remarkably consistent when 6.25mg/m^2 methotrexate was delivered using an Ommaya reservoir. Notably, ventricular and lumbar concentrations of methotrexate were maintained above the therapeutic concentration for at least 48 hours when using an Ommaya reservoir. They concluded that use of an Ommaya reservoir produces more consistent concentrations of methotrexate within the CSF. Other studies have also reported that 10% of lumbar punctures are misplaced, resulting in inadvertent injection of drugs into the epidural or subdural spaces [58]. Whilst Bleyer and colleagues showed that following intrathecal delivery of methotrexate, the ventricular concentration of methotrexate reaches just 10% of the lumbar concentration [36]. Together, these observations suggest that Ommaya reservoirs result in more reliable delivery plus significantly higher and more sustained methotrexate levels in the cerebral ventricles than the same dose of methotrexate delivered intrathecally. Since the current intrathecal doses are known to be efficacious in preventing CNS relapse, and there is a risk of neurotoxicity with high doses of methotrexate, this evidence supports a reduction of the methotrexate dose when an Ommaya reservoir is used.

2. *Use of lower doses of methotrexate via Ommaya reservoirs results in therapeutic CSF methotrexate levels in almost all patients*

A reduced dosing strategy was reported by Strother et al in 1989 for administration of methotrexate via Ommaya reservoir in 12 children with active meningeal leukaemia [49]. They monitored ventricular concentrations of methotrexate, utilising an approach where a smaller initial dose (4mg or 6mg) of intraventricular methotrexate is supplemented with further doses at 24 or 48 hours, titrated to maintain a therapeutic concentration of methotrexate above 1umol/L for 72 hours. An initial dose of 6mg methotrexate gave therapeutic CSF methotrexate levels in all CSF samples at 24 hours and three-quarters of samples at 48 hours. The authors

emphasised that there is significant intra- and inter-patient variability in the concentrations of methotrexate and encouraged the use of therapeutic drug monitoring to titrate doses to individual patient requirements. By using this approach, large initial doses of intraventricular methotrexate may be avoided without compromising efficacy.

3. *Frequent small doses of methotrexate via Ommaya may optimise pharmacokinetics*:

Earlier work by Bleyer and colleagues in 1978 demonstrated that severe neurotoxicity associated with high-dose methotrexate and large cumulative doses of methotrexate delivered to the CNS could be avoided by adopting a "Concentration x Time" (CxT) intraventricular treatment regimen. Here, smaller doses of methotrexate are given more frequently (1mg/12hr for 3 days, repeated weekly) to maintain a therapeutic concentration within the CSF (methotrexate concentration >1 μmol/L), while preventing severe neurotoxicity associated with larger, less frequent intraventricular doses (12mg/m^2, max dose of 15mg, twice-weekly) [36]. Importantly, the CxT protocol maintained methotrexate >1 μmol/L, in the therapeutic range [46], whereas the large-bolus regimen peaked shortly after administration, before becoming sub-therapeutic 32 hours after delivery [36]. Therefore, the CxT protocol demonstrated that smaller doses of methotrexate given intraventricularly at regular dosing intervals could eliminate high peak concentrations of methotrexate within the CNS (thought to be a risk factor for methotrexate-induced neurotoxicity), while maintaining adequate concentrations of methotrexate for the duration of the leukaemic cell cycle to optimise cytotoxicity. Strother and colleagues noted that studies have consistently failed to demonstrate correlation between higher initial methotrexate doses (12mg/m^2) and peak, 24- or 48- hour concentrations [35, 36, 47, 48]. They advocate a similar approach as Bleyer et al [36], where smaller initial doses are titrated based on CSF sampling to maintain methotrexate concentrations >1 μmol/L for at least 72 hours, thereby maximising therapeutic potential whilst minimising the risk of neurotoxicity.

Overall, these studies, whilst not conclusive, support reduced dosing for methotrexate administered via an Ommaya reservoir, and provide no evidence that use of higher doses leads to more sustained therapeutic levels in the CSF.

5. Other intrathecal drugs

No published literature is available on which to base dosing recommendations for the other commonly administered intrathecal drugs for ALL, namely hydrocortisone and cytarabine. Based on the discussion above, it seems reasonable to extrapolate findings from

pharmacokinetic studies of methotrexate to other anti-leukaemic drugs whose dosing was originally established for intrathecal use via lumbar puncture. Thus, we would advocate 50% dosing for all three drugs when triple intrathecal therapy is administered, although we note that this is not evidence-based. This is consistent with current recommendations on the Children's Oncology Group trials in the USA (information obtained from clinical trial protocols, unpublished).

6. Future recommendations:

In the absence of definitive level I evidence to guide clinical decision making, our recommendation is based on the available published evidence. Only centres with expert paediatric neurosurgeons and experience of implanting Ommaya reservoirs should attempt insertion. Adequate MRI neuroimaging of the brain and spinal cord should be carried out shortly before neurosurgical implantation. Adequate staff training, and a meticulous aseptic protocol should be followed to minimise the risk of CNS infection. Centres using Ommaya reservoirs should conduct continuous, thorough clinical audits to identify areas of clinical concern for directed improvement.

Overall, the literature supports dose reductions when using intraventricular methotrexate, compared with intrathecal methotrexate, owing to improved CSF distribution resulting in higher ventricular methotrexate concentrations. While CxT dosing regimens, with daily low-dose methotrexate [36] may produce optimal methotrexate concentrations, the safety and efficacy of this regimen has not been verified in a large cohort of children. Additionally, repeated Ommaya access is consistently associated with increased rates of infection [12]. As discussed above, in most children a single dose of 50% of the intrathecal dose led to sustained therapeutic concentrations in the CSF for at least 48 hours. Monitoring of levels and administration of top-up methotrexate at 24 and 48 hours could be considered best practice but since similar monitoring and dose modifications are not currently in place for intrathecal methotrexate, its adoption in front-line ALL CNS prophylaxis protocols could be considered a treatment escalation. Therefore, in these situations, we recommend that methotrexate via Ommaya reservoir be administered at 50% of the intrathecal dose, at the same treatment intervals without therapeutic drug monitoring. For patients with relapsed or refractory CNS leukaemia a fractionated CxT approach or use of 50% dosing with monitoring of levels and "top-ups" as needed should be considered on a case-by-case basis.

It is clear from the above that further research on this topic is required. Priorities for further investigation would a prospective registry of ALL patients with Ommaya reservoirs capturing indication, dosing regimen, complications and outcome. In addition, given the encouraging historical data suggesting that Ommaya reservoir use results in longer remission [43, 44] and may be preferred by patients [42], an RCT of Ommaya vs intrathecal methotrexate for relapsed CNS ALL (as part of a systemic multiagent chemotherapy approach) is desirable.

This data was presented and discussed at the UK Childhood Leukaemia Clinicians Network meeting on the 23rd May 2017. A pragmatic consensus decision was made to recommend administration of 50% doses of all intrathecal chemotherapy to any child requiring intraventricular administration of CNS-directed therapy on front-line ALL protocols, pending any further published evidence to guide rational evidence-based dosing.

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Ruairi Wilson, Caroline Osborne, and Christina Halsey declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

7. References:

1. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. Lancet Oncol. 2008;9(3):257-68.
2. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol. 2013;14(3):199-209.
3. Burger B, Zimmermann M, Mann G, et al. Diagnostic cerebrospinal fluid examination in children with acute lymphoblastic leukemia: significance of low leukocyte counts with blasts or traumatic lumbar puncture. J Clin Oncol. 2003;21(2):184-188.

4. Pui CH, Campana D, Pei D et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009;360(60):2730-2741.

5. Halsey C, Buck G, Richards S, Vargha-Khadem F, Hill F, Gibson B. The impact of therapy for childhood acute lymphoblastic leukaemia on intelligence quotients; results of the risk-stratified randomized central nervous system treatment trial MRC UKALL XI. J Hematol Oncol. 2011;4:42.

6. Veerman AJ, Kamps WA, van den Berg H et al. Dexamethasone-based therapy for childhood acute lymphoblastic leukaemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997-2004). Lancet Oncol. 2009;10(10):957-966.

7. Pui CH, Sandlund JT, Pei D et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. Blood. 2004;104(9):2690-2696.

8. Möricke A, Reiter A, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood. 2008;111(9):4477-4489.

9. Moghrabi A, Levy DE, Asselin B et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. Blood. 2007;109(3):896-904.

10. Ommaya AK. Subcutaneous reservoir and pump for sterile access to ventricular cerebrospinal fluid. Lancet. 1963;2(7315):983-984.

11. Meijer L, Walker D, SlavcI. Intra-Cerebrospinal Fluid Therapy for Leptomeningeal Metastases in Medulloblastoma. In: Dimitris A. Kombogiorgas, editor. The Medulloblastoma Book, Nova Science Publishers, Inc. 2014.

12. Peyrl A, Chocholous M, Azizi AA, Czech T, Dorfer C, Mitteregger D, Gojo J, Minichmayr E, Slavc I. Safety of Ommaya reservoirs in children with brain tumors: a 20-year experience with 5472 intraventricular drug administrations in 98 patients. J Neurooncol. 2014;120(1):139-145.

13. Mead PA, Safdieh JE, Nizza P, Tuma S, Sepkowitz KA. Ommaya reservoir infections: a 16-year retrospective analysis. J Infect. 2014;68(3):225-230.

14. Young GA, Milliken S, Jurd J, Poulgrain P, Vincent PC. The intraventricular reservoir in the treatment of neurological disease secondary to hematological malignancy: an eight year experience. Aust N Z J Med. 1986;16(3):373-377.
15. Lishner M, Perrin RG, Feld R, Messner HA, Tuffnell PG, Elhakim T, Matlow A, Curtis JE. Complications associated with Ommaya reservoirs in patients with cancer. The Princess Margaret Hospital experience and a review of the literature. Arch Intern Med. 1990;150(1):173-176.
16. Browne MJ, Dinndorf PA, Perek D, Commers J, Bleyer WA, Poplack DG, Pizzo PA. Infectious complications of intraventricular reservoirs in cancer patients. Pediatr Infect Dis J. 1987;6(2):182-189.
17. Bleyer WA, Pizzo PA, Spence AM, Platt WD, Benjamin DR, Kolins CJ, Poplack DG. The Ommaya reservoir: newly recognized complications and recommendations for insertion and use. Cancer. 1978;41(6):2431-2437.
18. Packer RJ, Zimmerman RA, Rosenstock J et al. Focal encephalopathy following methotrexate therapy: administration via a misplaced intraventricular catheter. Arch Neurol. 1981;38:450-452.
19. Colamaria V, Carabello R, Borgna-Pignatti C et al. Transient focal leukoencephalopathy following intraventricular methotrexate and cytarabine; a complication of Ommaya reservoir: case report and review of the literature. Child's Nerv Syst. 1990;6:231-235.
20. Kennedy BC, Brown LT, Komotar RJ, McKhann GM 2nd. Frameless Stereotactic Ommaya Reservoir Placement: Efficacy and Complication Comparison with Frame-Based Technique. Stereotact Funct Neurosurg. 2015:93(6);415-418.
21. Weiner GM, Chivukula S, Chen CJ, Ding D, Engh JA, Amankulor N. Ommaya reservoir with ventricular catheter placement for chemotherapy with frameless and pinless electromagnetic surgical neuronavigation. Clin Neurol Neurosurg. 2015:130;61-66.
22. Morgenstern PF, Connors S, Reiner AS, Greenfield JP. Image Guidance for Placement of Ommaya Reservoirs: Comparison of Fluoroscopy and Frameless Stereotactic Navigation in 145 Patients. World Neurosurg. 2016:93;154-158.
23. Inaba H, Khan RB, Laningham FH, Crews KR, Pui CH, Daw NC. Clinical and radiological characteristics of methotrexate-induced acute encephalopathy in pediatric patients with cancer. Ann Oncol. 2008;19:178-184.

24. Bhojwani D et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. J Clin Oncol. 2014;32(9):949-959.
25. Bond J, Hough R, Moppett J, Vora A, Mitchell C, Goulden N. 'Stroke-like syndrome' caused by intrathecal methotrexate in patients treated during the UKALL 2003 trial. Leukaemia. 2013;27(4):1765-9.
26. Cheung YT et al. Leukoencephalopathy and long-term neurobehavioural, neurocognitive, and brain imaging outcomes in survivors of childhood acute lymphoblastic leukaemia treated with chemotherapy: a longitudinal analysis. Lancet Hematol. 2016;3(10):e456-e466.
27. Schmiegelow K, Attarbaschi A, Barzilai S et al. Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. Lancet Oncol. 2016:17(6);e231-e239.
28. Krull KR et al. Chemotherapy Pharmacodynamics and Neuroimaging and Neurocognitive Outcomes in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia. J Clin Oncol. 2016;34(22):2644-2653.
29. Jacola LM et al. Longitudinal Assessment of Neurocognitive Outcomes in Survivors of Childhood Acute Lymphoblastic Leukemia Treated on a Contemporary Chemotherapy Protocol. J Clin Oncol. 2016;34(11):1239-1247.
30. Krull KR, Brinkman TM, Li C, Armstrong GT, Ness KK, Srivastava DK, Gurney JG, Kimberg C, Krasin MJ, Pui CH, Robinson LL, Hudson MM. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukaemia: a report from the St Jude lifetime cohort study. J Clin Oncol. 2013;31(35):4407-4415.
31. Kanellopoulos A et al. Neurocognitive Outcome in Very Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia After Treatment with Chemotherapy Only. Pediatr Blood Cancer. 2016;63(1):133-138.
32. Mahoney DH Jr, Shuster JJ, Nitschke R et al. Acute neurotoxicity in children with B-precursor acute lymphoid leukemia: an association with intermediate-dose intravenous methotrexate and intrathecal triple therapy--a Pediatric Oncology Group study. J Clin Oncol. 1998:16(5);1712-1722.
33. Forster VJ, van Delft FW, Baird SF, Mair S, Skinner R, Halsey C. Drug interactions may be important risk

factors for methotrexate neurotoxicity, particularly in pediatric leukemia patients. Cancer Chemother Pharmacol. 2016:78(5);1093-1096.

34. Goldie JH, Price LA, Harrap KR. Methotrexate toxicity: Correlation with duration of administration, plasma levels, dose and excretion pattern. Eur J Cancer. 1972:8(4);409-414.
35. Shapiro WR, Young DF, Mehta BM. Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. N Engl J Med. 1975;293(4):161-166.
36. Bleyer WA, Poplack DG, Simon RM. "Concentration x time" methotrexate via a subcutaneous reservoir: a less toxic regimen for intraventricular chemotherapy of central nervous system neoplasms. Blood. 1978;51(5):835-842.
37. Bostrom BC, Erdmann GR, Kamen BA. Systemic methotrexate exposure is greater after intrathecal than after oral administration. J Pediatr Hematol Oncol. 2003;25(2):114-117.
38. Thyss A, Suciu S, Bertrand Y et al. Systemic effect of intrathecal methotrexate during the initial phase of treatment of childhood acute lymphoblastic leukemia. The European Organization for Research and Treatment of Cancer Children's Leukemia Cooperative Group. J Clin Oncol. 1997;15(5):1824-1830.
39. Mehta BM, Glass JP, Shapiro WR. Serum and cerebrospinal fluid distribution of 5-methyltetrahydrofolate after intravenous calcium leucovorin and intra-ommaya methotrexate administration in patients with meningeal carcinomatosis. Cancer Research. 1983;43:435-438.
40. Ells LJ, Hancock C, Copley VR et al. Prevalence of severe childhood obesity in England: 2006-2013. Arch Dis Child. 2015:100(7);631-636.
41. Lakshman R, Elks CE, Ong KK. Childhood Obesity. Circulation. 2012:126(14);1770-1779.
42. Steinherz P, Jereb B, Galicich J. Therapy of CNS leukemia with intraventricular chemotherapy and low-dose neuraxis radiotherapy. J Clin Oncol. 1985:3(9);1217-1226.
43. Bleyer WA, Poplack DG. Intraventricular versus intralumbar methotrexate for central-nervous system leukaemia: prolonged remission with the ommaya reservoir. Med Pediatr Oncol. 1979;6:2017-213.

44. Iacoangeli M, Roselli R, Pagano L et al. Intrathecal chemotherapy for treatment of overt meningeal leukaemia: Comparison between intraventricular and traditional intralumbar route. Ann Oncol. 1995;6:377-382.

45. Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. Cancer. 1978: 41(1);36-51.

46. Hryniuk WM, Bertino JR. Treatment of leukemia with large doses of methotrexate and folinic acid: clinical-biochemical correlates. J Clin Invest. 1969;48(11):2140-2155.

47. Ettinger LJ, Chervinsky DS, Freeman AI, Creaven PJ. Pharmacokinetics of methotrexate following intravenous and intraventricular administration in acute lymphocytic leukemia and non-Hodgkin's lymphoma. Cancer. 1982;50(9):1676-1682.

48. Mauer AM. Cell Kinetics and practical consequences for therapy of acute leukaemia. N Engl J Med. 1975;293:389-393.

49. Strother DR, Glynn-Barnhart A, Kovnar E, Gregory RE, Murphy SB. Variability in the disposition of intraventricular methotrexate: a proposal for rational dosing. J Clin Oncol. 1989;7(11):1741-1747.

50. Kuo AH-M, Xenophon Y, Galicich H, Fried J, Clarkson BD. Proliferative kinetics of central nervous system (CNS) leukaemia. Cancer. 1975;36:232-239.

51. Tsuchiya J, Moteki M, Shimano S, Shinonome S, Suda T, Omine M, Maekawa T. Proliferative kinetics of the leukaemic cells in meningeal leukaemia. Cancer. 1978;42:1255-1262.

52. Brinker T, Stopa E, Morrison J, Klinge P. A new look at cerebrospinal fluid circulation. Fluids Barriers CNS. 2014:11;10.

53. Bleyer WA, Drake JC, Chabner BA. Neurotoxicity and elevated cerebrospinal-fluid methotrexate concentration in meningeal leukemia. N Engl J Med. 1973;289(15):770-773.

54. Ettinger LJ, Chervinsky DS, Freeman AI, Creaven PJ. Pharmacokinetics of methotrexate following intravenous and intraventricular administration in acute lymphocytic leukemia and non-Hodgkin's lymphoma. Cancer. 1982;50(9):1676-1682.

55. Morse M, Savitch J, Balis F, Miser J, Feusner J, Reaman G, Poplack D, Bleyer A. Altered central nervous system pharmacology of methotrexate in childhood leukemia: another sign of meningeal relapse. J Clin Oncol. 1985;3(1):19-24.

56. Grossman SA, Trump DL, Chen DC, Thompson G, Camargo EE. Cerebrospinal fluid flow abnormalities in patients with neoplastic meningitis. An evaluation using 111indium-DTPA ventriculography. Am J Med. 1982;73(5):641-647.
57. Chiro GD, Hammock MK, Bleyer WA. Spinal descent of cerebrospinal fluid in man. Neurology. 1976;26(1):1-8.
58. Larson S, Schall G, Di Chrio G. The influence of previous lumbar puncture and pneumoencephalography on the incidence of unsuccessful radioisotope cisternography. J Nucl Med. 1971;12:555–557.

Table 1: Advantages and limitations of using Ommaya reservoirs in place of repeated intrathecal injections for administering methotrexate to the CNS.

Advantages:	**Limitations:**
Ease of access to CSF for repeated drug delivery	**CNS infection risk**
Reduced risk of misplaced drug delivery	**Increased neuroimaging**
No requirement for general anaesthesia	**Risk of misplaced catheter**
Improved CSF distribution of drug	**Risk of tumour seeding (solid tumours)**
Possibly improved efficacy	**Bleeding risk**
CSF sampling allows for dose titration	**Risk of further neurosurgery**
Reduced frequency of lumbar puncture	**Risk of catheter occlusion**

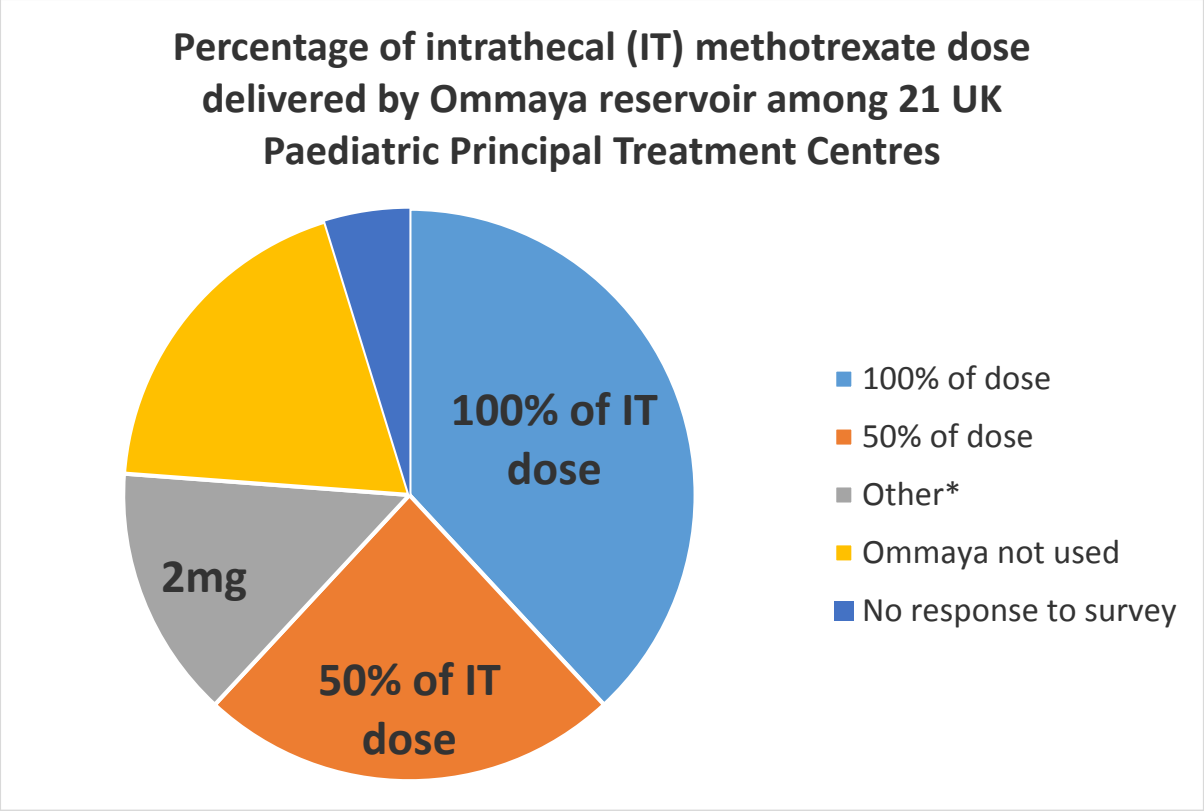

Figure 1: This pie chart represents the 20 responses obtained from our survey of 21 UK Paediatric Principal Treatment Centres. Dosing percentages are compared to age-appropriate intrathecal (IT) doses of methotrexate advocated in modern UKALL clinical trials. 8/21 centres used 100% of the intrathecal methotrexate dose when using an Ommaya reservoir for CNS access, 5/21 centres used 50% dosing, 3/21 centres previously used 2mg as a single dose, 4/21 centres did not use Ommaya reservoirs and 1 centre did not respond to our survey. *Of the 3 centres previously using 2mg dosing, they have advised that they have since changed their practice, with 2 centres now opting for 50% dosing and 1 centre now using 100% dosing.