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Neoplastic meningitis resulting from hematological malignancies: pharmacokinetic considerations and maximizing outcome

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Abstract

Neoplastic meningitis, also known as leptomeningeal metastases, is a complication of various types of cancer that occurs when tumor cells enter the cerebrospinal fluid (CSF), travel along CSF pathways and grow. Treatment options include drug delivery directly into the CNS or systemic administration for targeted action in the CNS. CNS drug delivery is limited by the blood–brain barrier and the blood–CSF barrier. It may be possible to partially overcome this by using high-dose systemic therapy; however, this is done at the possible expense of increased systemic toxicity. Intra-CSF drug delivery bypasses the blood–brain barrier and allows direct access of the chemotherapeutic agent to the CSF. Because neoplastic meningitis occurs in an increasingly large percentage of all cancer patients, it is imperative to optimize drug delivery to the CSF and meninges. Both the pharmacokinetic profile of the chemotherapeutic agent and the site of administration influence therapeutic efficacy. Achieving prolonged therapeutic cytotoxic drug concentrations and even distribution in the CSF will improve efficacy. In this article we summarize data on the efficacy, safety and outcome of high-dose systemic and intra-CSF treatments.

Keywords

hematological malignancy; high-dose systemic; intracerebrospinal fluid; leptomeningeal metastases; neoplastic meningitis; pharmacokinetics

Neoplastic meningitis (NM) is often a late-stage complication of cancer whereby malignant cells spread to the leptomeninges and subarachnoid space [1,2]. The leptomeninges include both the arachnoid membrane and the pia mater. The sub-arachnoid space lies between these two layers and contains the cerebrospinal fluid (CSF) [3]. The blood–CSF barrier is located at the level of the choroid plexus, and at the level of the arachnoid membrane.

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In NM due to leukemia or lymphoma, the mechanism of NM is infiltration and penetration of tumor cells through the blood vessels of the arachnoid and choroid plexus. In NM, tumor cells that penetrate to the CSF ultimately spread throughout the entire neuroaxis (Figure 1A). Although NM usually presents in patients with widely disseminated and progressive systemic cancer, it can be an early occurrence in patients with aggressive malignancies (e.g., Burkitt's lymphoma) [4,5]. The incidence of NM has been estimated from retrospective studies and may vary as a function of tumor type, tumor location, patient age and the extent of disease [6]. In addition, the overall incidence is increasing as cancer patients live longer [2].

Epidemiology

CNS involvement in adults with newly diagnosed acute lymphoblastic leukemia (ALL) has been estimated to be less than 10%, whereas the incidence may approach 12% in pediatric patients [7]. Epidemiological reports of CNS metastasis in patients with recurrent ALL have a high degree of variability, ranging from 3–25% of patients [8–10]. The incidence of CNS involvement in adult patients with acute myeloid leukemia is generally lower than in pediatric patients with acute myeloid leukemia (2–7% vs 5–29%, respectively) [7]. Lymphomatous meningitis (the seeding of the leptomeninges in patients with lymphoma) in patients with non-Hodgkin's lymphoma ranges from 1–20% [8,9]. Clinical risk factors for CNS involvement in non-Hodgkin's lymphoma include raised serum lactate dehydrogenase, low serum albumin, age greater than 60 years, involvement of the testes, breast or bone marrow, or the involvement of greater than one extranodal site [1,10,11]. Lymphomatous meningitis can also be detected in approximately 21% of patients with primary CNS lymphoma [12]. The incidence of leukemic NM was reduced considerably by introducing CNS prophylaxis strategies [13–15].

Clinical features

The clinical features of NM are typically multifocal, and depend on which areas of the nervous system are involved. Brain involvement can present as encephalopathy, while cranial nerve involvement can result in dysphagia, diplopia, dysarthria, visual loss and hearing loss [5]. Spine and spinal nerve involvement can cause back pain, sacral and perineal numbness, bowel and bladder dysfunction and extremity weakness. NM causes symptoms due to infiltration into the arachnoid and into the parenchyma, via progression of tumor cells in the perivascular space of penetrating vessels. Alterations in CSF flow (e.g., a block or hydrocephalus) are common and may result in headache, nausea and vomiting [16].

Apart from neurological considerations in patients with NM, the discovery of NM may suggest the likelihood of an impending systemic relapse, which itself carries negative prognostic significance.

Diagnosis

The diagnosis of NM is unequivocally established by demonstration of malignant cells in the CSF. However, false-negative CSF cytology is common and can occur in up to 45% of patients after a single lumbar puncture [5]. By the third lumbar puncture the diagnostic yield increases to 90% [17]. Viral infections of CNS and paraneoplastic syndromes can, on rare occasions, lead to a spurious diagnosis of malignancy, namely lymphoma [17,18]. Disproportionate elevation of specific tumor markers, such as β -human chorionic gonadotrophin in choriocarcinoma and carcinoembryonic antigen in colorectal cancer is usually diagnostic of NM. Nonspecific markers include β -glucuronidase, lactate dehydrogenase and CSF protein, which can also occasionally be elevated in case of infection or inflammation [17]. MRI can show enlargement or enhancement of the cranial or spinal

nerves, superficial linear leptomeningeal enhancement, nodular intradural enhancement and hydrocephalus.

Treatment overview

In patients with NM, the primary goals of treatment include palliation, delay of further neurological deterioration and maintenance of quality of life [2,19]. An early diagnosis of NM is critical, especially in patients who present with few or no neurological deficits and a low CNS tumor burden, so as to achieve a better treatment response and improve survival [1,20]. While treatment is mainly palliative in patients with relapsed disease, a more intensive approach may be used in patients with CNS involvement at the time of diagnosis, or even possibly at first relapse [21]. A combined treatment strategy may include local (intrathecal) therapy as an adjunct to multidrug systemic regimens. Radiotherapy (RT) is also used in palliation of NM, mainly for focal disease or rapidly progressive cranial nerve palsies [17,22]. In addition to treatment of neoplasm, addressing hydrocephalus via ventriculoperitoneal shunting is feasible and may improve outcome [23].

The treatment modality utilized, and the order in which treatments are selected, depend on the radiographic pattern of NM (nodular vs linear), the degree to which the CNS is affected (extensive vs limited) and, most importantly, after careful consideration of the most disabling neurological symptoms. Treatment of bulky, nodular disease generally requires some form of systemic chemotherapy or RT, since intra-CSF chemotherapy does not penetrate into the tumor beyond a few cell layers.

Radiotherapy can be utilized in various ways in treating NM, and can yield quicker results than chemotherapy for many patients. While whole-brain RT is often used to stabilize intracranial disease, it does not prevent or treat spinal involvement of NM and carries the risk of neurocognitive toxicity. Craniospinal RT involves the risk of depleting adult bone marrow reserves, limiting the subsequent use of chemotherapy and is not recommended for most patients with NM [17,22]. Limited-field RT is often utilized in palliation of spinal symptoms, such as dermatomal pain. Improvement in CSF flow after treatment of a site of obstruction with focal RT, when assessed with radioisotope flow studies, may lead to an improved outcome in NM [24,25].

A recently completed multicenter retrospective study demonstrated the feasibility and possible benefit of ventriculoperitoneal shunting in conjunction with intraventricular chemotherapy. These patients were still able to receive intraventricular chemotherapy due to the placement of an on/off valve [23].

Most systemic chemotherapeutic agents, including methotrexate, the most commonly used agent in this setting, only penetrate the CNS in limited quantities. As such, systemic cytotoxic drugs must be administered at high doses to cross the blood–brain barrier (BBB) and allow sufficient quantities to reach the CSF compartments [1]. As illustrated in Figure 1B, the BBB is comprised of endothelial cells arranged in a complex of tight junctions between cells that restrict the free passage of molecules. A second major barrier system in the brain, the blood–CSF barrier, is composed of the epithelial cells of the choroid plexus, the major site of CSF production (Figure 1C), and the arachnoid and arachnoid vasculature. The choroidal epithelium affects drug delivery to and elimination from the CSF [18]. Different drugs may penetrate these two barrier systems to different degrees; by flooding the barriers with high systemic dosing, CNS penetration may improve, but at the risk of increased systemic toxicity. In addition, prophylactic systemic therapy treats subclinical NM where the blood–CSF barrier and the blood–brain barrier are still intact.

An alternative therapeutic approach involves direct intra-CSF delivery either by a lumbar puncture (intralumbar) or a ventricular access device (intraventricular). This method circumvents the limitations associated with the passage of drugs across the BBB but raises issues concerning drug half-life, volume of distribution and clearance rates from the CSF [19]. Intra-CSF chemotherapy (depending on the site of administration) introduces the additional risks of surgery, anesthesia, infection, bleeding and chemical meningitis.

A drug's pharmacokinetic characteristics can clearly affect its utility. The short half-lives of conventional agents routinely used in intra-CSF therapy (e.g., methotrexate, cytarabine [Ara-C] and thiopeta) necessitate frequent dosing, which may be inconvenient for both the patient and the clinician. On the other hand, medications that can maintain prolonged cytotoxic levels in the CSF will reduce the frequency of dosing and may be an attractive alternative for the effective treatment of NM.

Given the low proliferative index of malignant cells in the CNS, their susceptibility to cytotoxic treatment may be theoretically increased by longer exposure times [26]. The improved pharmacokinetic profiles of sustained-release formulations may improve the clinical efficacy of intra-CSF drugs and minimize the side effects associated with systemic toxicity. It is important to consider that the placement of an Ommaya reservoir carries the additional risk of anesthesia, catheter misplacement, obstruction and infection of an indwelling device [5]. Except where indicated, the option of intra-CSF chemotherapy is generally based on expert opinion reviewing class 2A data, such as indicated in the National Comprehensive Cancer Network guidelines [27]. For many reasons, including the difficulty of performing clinical trials in this patient population, there is a paucity of class I data favoring the use of intra-CSF chemotherapy for most indications [5]. This review will highlight the pharmacokinetic and safety considerations associated with the treatment of NM, with particular emphasis on patients with lymphoma or leukemia.

Systemic versus intra-CSF chemotherapy

Both systemic chemotherapy and intra-CSF chemotherapy have unique theoretical advantages in treating patients with NM. Both treatment modalities have limited benefit given the overall poor prognosis of this group of patients.

System chemotherapy avoids the need for a periodic invasive procedures (such as lumbar puncture) and avoids the need for neurosurgical placement of an Ommaya reservoir. Intra-CSF therapy has limited utility in patients with bulky disease, where CSF flow may be altered. Bulky disease can prevent even distribution of intrathecal chemotherapy. In addition, there is risk of locally higher concentrations and higher risk of neurotoxicity. Some studies did not demonstrate a clinical benefit for adding intra-CSF chemotherapy to systemic chemotherapy; patients receiving the latter treatment may have experienced additional, and potentially unnecessary, toxicity [5,28].

However, the ability to attain cytotoxic levels of chemotherapy in CSF is likely to be limited for most useful systemic chemotherapy agents. The ability to achieve cytotoxic CSF levels by bypassing the BBB, represents the single most important advantage of intra-CSF chemotherapy. The properties of specific intra-CSF agents are outlined below.

Pharmacokinetic considerations

Since the CSF distributes cells throughout the craniospinal axis, malignancy can occur at any site. Consequently, a chemotherapeutic agent must be distributed consistently and evenly throughout the CSF to reach and treat multiple metastatic sites or to reach sites distant from where intra-CSF therapy is administered. Tumor killing and side-effects are

dependent on two factors: the concentration of chemotherapy achieved in the CSF and the amount of time that the chemotherapy is present in the CSF. Both of these factors can be manipulated to achieve optimal results [29]. Both intra-CSF and systemic chemotherapy may be required to effectively treat leptomeningeal and parenchymal metastases. Combining the most appropriate systemic chemotherapy for the primary cancer with the most effective intra-CSF therapy for leptomeningeal involvement may offer the most opportunities for improving efficacy [30].

Systemic chemotherapy

Systemic chemotherapy as a potential treatment option for NM offers some advantages over intra-CSF therapies. For example, CSF flow obstruction is a common occurrence in NM and may limit the dissemination of drug administered directly into the CSF compartment [1,6,31]. This issue is better studied in solid tumors; it is unclear if abnormal CSF flow occurs to the same extent in NM associated with leukemia. In the setting of NM, the blood–CSF barrier can be disrupted [32], potentially allowing the CSF to achieve higher concentrations of drug compared with the non-NM setting. Following intravenous delivery, only a few agents have been shown to achieve cytotoxic concentrations in the CSF with acceptable systemic toxicity.

High-dose methotrexate—Methotrexate acts as a competitive inhibitor of folic acid reductase, an enzyme required for the synthesis of the nucleoside thymidine. Consequently, methotrexate acts as an inhibitor of DNA synthesis. Methotrexate will have its greatest cytotoxic effects in rapidly dividing cells, such as cancer cells [33]. The precise dose of methotrexate that constitutes a ‘high dose’ is not well defined in the literature. Doses greater than 3 g/m² are required to achieve cytotoxic levels in the CSF [34,35]. At a systemic dose of 8 g/m², methotrexate concentrations in the CSF remain greater than 1 μmol/l for 48 h on average, and greater than 0.1 μmol/l for 93.3 h on average [30]. Despite clinical application for more than five decades, the use of high-dose methotrexate remains controversial, particularly for the treatment of pediatric patients with ALL [36–38]. Moreover, high-dose methotrexate involves the expense and inconvenience of hospitalization. Common side effects include nausea, vomiting and myelosuppression. The risk of renal failure resulting from intratubular precipitation of drug can be decreased by maintaining a high urine output and by urine alkalinization. Leukovorin rescue also helps to decrease the systemic toxicity from methotrexate.

High-dose Ara-C—Ara-C is metabolized intracellularly into its active triphosphate form (cytosine arabinoside triphosphate). Because this metabolite inhibits DNA polymerase by competing with the physiologic substrate deoxycytidine triphosphate, the cell cycle is arrested in S phase [39]. High-dose Ara-C is usually delivered in doses of 2–3 g/m² twice daily for 8–12 doses [40]. Severe neurotoxicity, however, limits the clinical utility of this approach. Another key disadvantage associated with systemic Ara-C therapy is the difficulty associated with the accurate measurement of CSF concentrations; the rapid elimination and metabolism of Ara-C to inactive uracil arabinoside may result in imprecise CSF measurements [35,40].

Other systemic agents—Several other systemically administered drugs can achieve therapeutic CSF levels including thiopeta, topotecan and etoposide, mafosfamide, busulfan, deoxyuridine, sodium iodide and iodine antibody. Noncytotoxic therapies include rituximab and trastuzumab.

Intra-CSF chemotherapy

The primary rationale for intra-CSF therapy is based on the assumption that it is difficult to achieve sustained therapeutic drug levels in the CSF via systemic administration without a significant risk of systemic toxicity [5]. Intra-CSF chemotherapy may be given via either the intralumbar (via lumbar puncture) or intraventricular (via Ommaya reservoir) route. The latter technique introduces the additional risk of anesthesia, intraventricular catheter misplacement (3–12%), catheter obstruction and infection (2–13%) [5]. Chemical meningitis may result from either route and can usually be managed in the outpatient setting with oral corticosteroids [21]. Lumbar delivery, while less invasive, introduces the increased risk of misinjection, an occurrence which is usually inapparent to the person performing the procedure. Drug distribution is poorer, particularly over the ventricles. Both of these factors likely contribute to the decreased survival observed in patients receiving intralumbar chemotherapy [31,41–43]. Serial lumbar puncture is associated with greater long-term discomfort and inconvenience than with use of an Ommaya reservoir [21,39,44]. However, as there is no indwelling hardware, the risk of infection is lower with intralumbar chemotherapy.

Methotrexate—This is the chemotherapeutic agent most commonly used for intra-CSF administration in patients with NM [2]. The minimal cytotoxic, or therapeutic, concentration is generally accepted to be greater than 1 $\mu\text{mol/l}$ [39], and a 10- to 12-mg dose administered twice-weekly can result in therapeutic concentrations in the CSF for up to 48 h [2,45]. Following a single intrathecal administration, Bleyer *et al.* demonstrated a biphasic elimination curve, with an initial half-life of 4.5 h and a terminal half-life of 14 h [46]. Mean methotrexate concentrations of greater than 10 $\mu\text{mol/l}$ were achieved at 6 h, and minimal cytotoxic drug concentration still remained at 24 h. At 48 h, the mean concentration in the lumbar CSF dropped by an order of magnitude below the accepted therapeutic range (0.1 $\mu\text{mol/l}$) [39,46].

The intraventricular route generally is considered more effective than the intralumbar route for delivering methotrexate to the CSF due to lower inter-individual variability in drug concentration [41–43]. The difference in benefit appears to be more pronounced for short-acting agents such as methotrexate [47]. With the intraventricular route, a mean ventricular CSF peak concentration of greater than 200 $\mu\text{mol/l}$ can drop to 0.2 $\mu\text{mol/l}$ at 48 h [39,42]. Evaluation of the corresponding lumbar CSF values showed detectable methotrexate levels after 1 h, and values exceeded the corresponding ventricular values by 4 h (at 4 h: 50 $\mu\text{mol/l}$; Table 1) [7,39,46,48–56]. Distribution and elimination appear to follow first-order kinetics, where CSF concentrations have been reported to be proportional to dose over a wide intra-CSF dosage range [39].

Unencapsulated Ara-C—Drug concentrations between 0.4 and 1.0 $\mu\text{mol/l}$ are considered to be therapeutically effective [39,49]. Following a single intraventricular dose of 30 mg, mean peak ventricular CSF concentrations of greater than 2 mmol/l have been reported, and cytotoxic concentrations were maintained for at least 24 h [49,54]. Ara-C elimination follows a biphasic elimination curve, with a 1 h mean initial half-life and a mean terminal half-life of 3.4 h [49]. Elimination kinetics are much faster with Ara-C than with methotrexate; therefore, more frequent dosing is required to maintain adequate cytotoxic drug levels in the CSF over time. Additional pharmacokinetic parameters are provided in Table 1. As with methotrexate, first-order distribution kinetics are observed within the dosage range of 15–100 mg. The activity of cytidine deaminase, which metabolizes Ara-CTP to Ara-U, is low within the CSF compartment compared with serum; therefore, Ara-C metabolism in the CSF is not of major concern. Elimination of Ara-C from the CSF is

primarily influenced by the CSF bulk flow rate, with a terminal half-life that is eight-times longer than in the plasma [39].

Thiotepa—An alkylating agent, thiotepa crosslinks DNA strands, preventing strand separation and the synthesis of DNA, RNA and protein [57,58]. It is a highly lipid soluble, non-polar agent that easily crosses the BBB and rapidly exits the CSF. Given the extremely rapid rate of adsorption (CSF half-life of only a few minutes), all sites of meningeal disease may not receive adequate drug exposure to achieve therapeutic efficacy. Practical issues associated with this short half life include the need for administration two- to three-times per week. Indeed, a preclinical study reported that peak ventricular levels were greater than 100 mg/ml in the ventricle but were less than 10% in the lumbar CSF only 1 h after intraventricular administration of 1 mg of thiotepa [55]. This study also concluded that the CSF clearance exceeded the rate of CSF bulk flow. Thiotepa may be considered for patients for whom prior methotrexate has failed; however, systemic administration may be preferred to intra-CSF routes of delivery. Additional pharmacokinetic parameters are given in Table 1.

Liposomal Ara-C—A sustained-release formulation of Ara-C, liposomal Ara-C has been designed to overcome the pharmacokinetic limitations associated with other intra-CSF chemotherapeutics. Ara-C is encapsulated in spherical, multivesicular lipid-based particles (~20 µm) and is released over a prolonged period of time after biodegradation of the lipid membranes (Figure 2). Liposomes are self-assembling colloidal structures composed of lipid bilayers surrounding an aqueous core [59,60]. Drug encapsulation within these liposomes provides a vehicle for sustained and gradual drug delivery. Packaging within fused nonconcentric vesicles, each with an internal aqueous chamber containing encapsulated drug solution surrounded by a lipid bilayer membrane, results in a multiple-fold increase in the drug's half-life [61]. A nearly 30-fold enhancement of the terminal half-life may be achieved with this multivesicular liposome technology versus conventional formulation by extending the half-life of Ara-C from 3.4 h (conventional formulation) to 5.9–82.4 h (liposomal formulation) [35,62,63]. Intra-CSF administration of liposomal Ara-C has a favorable pharmacokinetic profile whether administered via lumbar puncture or intraventricularly. The benefits of liposomal packaging include less frequent dosing and the potential for more uniform drug distribution throughout the neuroaxis as compared with free substances [64]. Liposomal Ara-C maintains cytotoxic concentrations for up to 2 weeks and, therefore, is administered twice-monthly rather than twice-weekly, as are methotrexate and unencapsulated Ara-C [2].

Diaziquone—This alkylating agent is designed for increased penetration across the BBB. Systemic administration results in a CSF:plasma ratio over 1.0 [65]; however, systemic toxicity has precluded the further development of this drug for intravenous use. A Phase I/II clinical trial of this agent for NM suggested that the agent was well tolerated at lower doses, with a 62% overall response rate lasting a median of 3 months [66,67].

Etoposide—This is a semisynthetic podophyllotoxin that functions as an inhibitor of topoisomerase II [68]. The drug is used in the treatment of many malignancies, including lymphomas and brain tumors. When compared with standard intra-CSF agents, etoposide offers a unique mechanism of action. Several feasibility studies have been performed that demonstrate the possibility of administering intra-CSF etoposide for neoplastic meningitis [69–71]. There were significant differences in CSF pharmacokinetics between individual patients with a median half-life of 9.65 h. The efficacy and toxicity of intra-CSF etoposide was comparable with standard intra-CSF agents but, based on these studies, does not appear to result in an improved outcome [71].

Rituximab—This anti-CD20 monoclonal antibody is frequently used intravenously for the treatment of B-cell lymphomas and leukemias. Several case reports, and the results of a completed Phase I trial, suggest the potential of using intra-CSF rituximab for lymphomatous meningitis [72–75]. As with other human monoclonal antibody agents, the penetration of rituximab into cerebrospinal fluid is quite poor, with CSF levels measured at 0.1% of the serum level [76]. Durable responses with intra-CSF rituximab have been described with and without the co-administration of systemic chemotherapy [74]. Doses ranging from 10 to 50 mg have been used, with increased toxicity occurring at doses above 25 mg. At the 25 mg dose, the mean 1 h peak CSF level was 472 µg/ml with a mean half-life of 34.9 h [75]. Reported adverse events include nausea, vomiting, headache, hypertension, diplopia, sustained upgaze and back pain. Premedication with acetaminophen, diphenylhydramine and famotidine have been used to increase tolerability. The preparation of rituximab with preservative-free diluents (i.e., sterile water) is important in minimizing CNS toxicity from this agent.

Efficacy data

In patients with ALL or lymphoma, intrathecal methotrexate remains the most commonly used drug for CNS treatment or prophylaxis [2]. Few prospective trials have evaluated the efficacy of treatments in patients with leukemia or lymphoma with CNS metastases, including NM. Furthermore, there are few guidelines for directing the appropriate choice of therapy [5,27]. To date, one randomized Phase III study (n = 28) has shown a significantly higher response rate in patients with lymphomatous meningitis receiving liposomal Ara-C versus unencapsulated Ara-C (71 vs 15%, respectively; $p < 0.006$) [64]. In this study, all patients treated with liposomal Ara-C completed the induction phase of therapy, whereas just over half (53%) of those receiving free Ara-C did so. The median times to neurologic progression for patients on the liposomal Ara-C and free Ara-C arms were 78.5 and 42 days, respectively. However, this difference in time was not statistically significant. Patients in the liposomal arm had improved performance status, and this was statistically significant. However, this trial did not include a comparison with methotrexate, which is a typical treatment for lymphomatous meningitis. Because some neurologic findings worsened whereas others improved, the percentage of patients whose neurologic status improved could not be adequately determined [64]. In a recent retrospective analysis of 55 patients with CNS involvement from lymphoma, the authors concluded that liposomal Ara-C is an effective and safe treatment alternative for this particular patient population [19]. Of these patients, 65% had diffuse large B-cell lymphoma (64% had stage IV disease at diagnosis). All patients received at least one cycle of intrathecal liposomal Ara-C; 45 of the 55 patients also received some other form of systemic therapy. A complete neurologic response was seen in 50% of patients and a partial neurologic response was achieved in another 22%. When present, a cytological response was generally seen following two to three doses. Safety data were also favorable, with 30 patients reporting no side effects. The most commonly reported adverse event was headache. Prospective trial data are urgently needed to further evaluate the tolerability and safety of this extended-release Ara-C formulation, especially when combined with high-dose systemic therapy.

Safety considerations

Justifiable concerns have recently been raised regarding the timing of sustained-release drug administration (e.g., liposomal Ara-C) [77,78]. If administration follows high-dose systemic chemotherapy over a sufficiently small time interval, the combined effect of a sustained-release formulation may contribute to an increased risk of severe neurologic side effects. Such an occurrence was recorded in a prospective trial using liposomal Ara-C in the prophylactic treatment setting [77]. A total of 33 patients with previously untreated ALL or

lymphoma received high-dose systemic therapy, including methotrexate and Ara-C, followed by intrathecal liposomal Ara-C after an interval of 7 days. Serious neurotoxicity occurred in five patients within 2 weeks of the last intrathecal dosing [77]. It has been postulated that intrathecal liposomal Ara-C may have contributed to neurologic side effects in two patients with refractory NM who had received prior intensive CNS-directed therapy [79]. However, others have suggested that the combination of intra-CSF liposomal chemotherapy with high-dose systemic chemotherapy (methotrexate at 8 g/m²) involves acceptable toxicity [80].

It is also unclear how safe it is to administer intra-CSF chemotherapy concurrently with RT, given the likelihood of combined neurotoxicity. Preliminary data suggests that this combination (using whole brain RT) might be feasible from a safety point of view [22,81]. Excessive toxicity has been reported with the concurrent administration of intra-CSF liposomal Ara-C with spinal RT [82].

Given the extended pharmacokinetics of liposomal Ara-C, these reports clearly underscore the inherent challenges in treating this difficult patient population. Clear identification of the underlying causes of these complications and the appropriate modification of treatment regimens is of paramount importance. Despite obvious concerns over neurological side effects, prudence should be exercised before ruling out potentially promising therapies [7,83,84].

Another important safety consideration relates to CSF flow obstructions commonly found in patients with NM. Obstructions in the subarachnoid, ventricular or spinal CSF flow pathways that are due to adhesions or tumors/metastases can lead to reduced drug clearance and high local drug concentrations. Because patients who experience inconsistent drug distribution are at high risk of acute or delayed neurotoxicity, intra-CSF administration should be avoided, or the dose should be appropriately adjusted for the altered volume of distribution [2,6]. Radioisotope CSF flow studies are helpful in determining the nature of CSF flow and adjusting therapy [16,24,25,85,86].

In very sick patients, safety concerns must always be carefully evaluated against the value of treatment. The intensity of CNS-directed therapy depends on the individual risk profile of the patient, the type and aggressiveness of the underlying hematologic malignancy, and the presence or absence of malignant cells in the CSF [2]. Treatment intensity and goals also depend on the stage of disease; treatment is often more aggressive in newly diagnosed patients, whereas it is often conservative in patients with multiple relapses.

Although concerns regarding the safety of liposomal Ara-C have been raised, clinicians should consider that similar neurologic side effects have been observed following systemic and intrathecal administration of both methotrexate and Ara-C [7]. Clinicians should also bear in mind that prospective trial data regarding safety outcomes are sparse. Because it is very difficult to assess safety concerns when there are also contributions from previous and simultaneous systemic chemotherapies, upcoming clinical trials need to address two important issues: the number of doses administered and the interval between combined liposomal Ara-C and high-dose systemic therapy [84].

Future perspective

Neoplastic meningitis is a serious complication that occurs in a significant number of patients with lymphoma and leukemia, but it is underdiagnosed [22], and the optimum treatment strategy is poorly defined. The pharmacokinetic properties of systemic and/or intra-CSF therapies for NM must be carefully evaluated in relation to the patient's primary chemotherapeutic regimen, stage of disease and aggressiveness of the underlying systemic

malignancy. Sustained-release medications have pharmacokinetic profiles that aim to improve efficacy and avoid systemic toxicities. Patients should benefit from less demanding dosage schedules made possible by the administration of sustained-release formulations of cytostatic drugs. Nevertheless, definitive statements regarding potential benefits await future trials. Although designing appropriately powered prospective trials represents a significant challenge, such trials are essential to effectively evaluate whether the favorable pharmacokinetic profile of sustained-release formulations translates into superior clinical efficacy and safety (e.g., improved survival time and quality of life and reduced toxicity) in the treatment of NM resulting from hematological malignancies. The development of an NM registry for hematologic cancers may help to further define the frequency of NM and the characteristic symptomatology, identify patient populations that would benefit most from intra-CSF treatment and define how effectively intra-CSF treatments are used.

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Executive summary

- Neoplastic meningitis is an aggressive condition involving tumor cells that invade the cerebrospinal fluid and the meninges.
- Treatment options for neoplastic meningitis include radiotherapy, systemic chemotherapy and intrathecal chemotherapy.
- The efficacy of a chemotherapeutic agent is dependent upon the site of administration and the pharmacokinetic profile of each drug.
- Prolonged drug concentration and cerebrospinal fluid distribution are important factors in cytotoxic effect.

Figure 1. Cerebrospinal fluid flow, the blood–brain barrier and the blood–cerebrospinal fluid barrier

(A) Within the ventricular system, the CSF is primarily made up of cells of the choroid plexus, which line the roofs of the third and fourth ventricles and the lateral walls of the lateral ventricles. Once CSF exits the fourth ventricle and enters the subarachnoid space, it is able to flow freely around the spinal cord or over the cortical convexities. When tumor cells gain access to the leptomeninges, they spread diffusely throughout the entire subarachnoid space of the neuroaxis by the constant flow of CSF. Tumor cells reach the subarachnoid space through the blood, by growing along nerve and vascular sheaths or by migration from an adjacent tumor. (B) Drug distribution to the CSF space and to the brain parenchyma is partly limited by the presence of the blood–brain barrier and the blood–CSF barrier. The blood–brain barrier is located between the blood and the extracellular space of the brain and is formed by the capillary endothelial cells that lack fenestrations and have tight intercellular junctions. (C) The blood–CSF barrier consists of the epithelial cells of the choroid plexus that are partially able to prevent drug delivery to the CSF and to eliminate drugs from the CSF.

CSF: Cerebrospinal fluid.

Figure 2. Liposomal packaging for chemotherapeutic drug delivery

(A) Unilamellar vesicles contain a single internal aqueous compartment and typically have a diameter of 0.02–0.5 μm . (B) Multilamellar vesicles contain multiple concentric internal aqueous compartments in an onion-skin arrangement and typically have a diameter of 0.2–5 μm . (C) Multivesicular liposomes are structurally distinct from lamellar liposomes. They consist of an aggregation of numerous nonconcentric internal compartments that are separated by bilayered liquid septa. These particles, which generally have a total diameter of approximately 3–30 μm , but may be as large as 100 μm in diameter, consist of hundreds of drug-filled aqueous chambers in a honeycomb-like arrangement. After intrathecal injection, the biodegradation of the lipid membranes at body temperature leads to a gradual release of drug, ensuring prolonged cytotoxic drug concentrations in the cerebrospinal fluid.

Table 1

Pharmacokinetics of intracerebrospinal fluid chemotherapies.

PK parameter	Methotrexate	Cytarabine	Thiotepa	Liposomal cytarabine
Cytotoxic concentration	>1 µmol/l [18]	0.4–1.0 µmol/l [18,36–38]	–	0.1 mg/l [39]
Elimination (single dose intralumbar or intraventricular)	Biphasic [32] Initial: 4.5 h Terminal: 14 h	Biphasic [37] Initial: 1 h Terminal: 3.4 h	Terminal: 1 h [18]	Biphasic Initial: 7.2 h Terminal: 140 h [7,40] Terminal: 227 h (lumbar) 130 h (ventricular) [40] Pediatric Terminal: 50–57 h (ventricular) [41]
Intralumbar dose, mean concentrations	Lumbar [18,32] 6 h: >10 µmol/l 24 h: >1 µmol/l 48 h: 0.1 µmol/l Ventricular [18,32] Variable ~10% of lumbar	–	–	Ventricular CSF [†] [40] C _{max} : 83 mg/l Lumbar CSF C _{max} : 2890 mg/l
Intraventricular dose, mean concentrations	Ventricular CSF [18,32] Peak: >200 µmol/l 48 h: 0.2 µmol/l Lumbar CSF [18,32] 1 h: detectable 4 h: 50 µmol/l	Ventricular CSF Peak: >2 mmol/l >24 h: 1 µmol/l [37,42] Lumbar CSF 3–4 h: detectable	Ventricular CSF [18] 2 h: 10 µg/ml 8 h: 1 µg/ml Lumbar CSF 1 h: ~10% of ventricular	Ventricular CSF [†] [40] C _{max} : 554 mg/l Lumbar CSF C _{max} : 68.5 mg/l
Mean AUC (CSF)	–	354 mmol/min/l	Ventricular [18] 5470 µg/min/ml Lumbar ~5% of ventricular AUC	Ventricular 4120 µg/h Lumbar 598 µg/h [†] [40]
Mean CSF clearance	–	0.42 ml/min [18]	1.8 ml/min [18,43]	Ventricular 4120 µg/h Lumbar 598 µg/h [†] [40]
Mean distribution volume (l)	0.48 [18]	0.055 [18]	–	0.15–0.28 [†] [40,44]

[†]Total cytarabine.

AUC: Area under the curve; CSF: Cerebrospinal fluid; PK: Pharmacokinetic.