Treatment of lymphomatous and leukemic meningitis with liposomal encapsulated cytarabine

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Abstract: Liposomal encapsulated cytarabine (DepoCyte®, Mundipharma GmbH, Limburg/Lahn, Germany) is a slow-release formulation of conventional cytarabine. It is licensed for intrathecal use in patients with lymphomatous and leukemic meningitis. DepoCyte® obtained superior response rates, improved patient quality of life and improved the time to neurological progression in a randomized albeit small clinical trial. In this review we briefly summarize the clinical data and discuss them in light of clinical problems and possible treatment scenarios.
Keywords: liposomal cytarabine, leukemic meningitis, lymphomatous meningitis

Introduction – liposomal encapsulated anti-cancer drugs

In an attempt to address some of the problems associated with the lack of tumor selectivity and stability of conventional cytostatic drugs, a variety of novel drug delivery systems has been developed. Of these, liposomal drug carrier systems represent a mature and versatile technology, and several liposomal formulations of anti-cancer drugs have been approved for cancer chemotherapy or are in advanced stages of clinical development.

Liposomes are self-assembling colloid structures composed of lipid bilayers surrounding aqueous compartments. They were first described by Bangham et al (1965) in the mid 1960s and were initially used as a model system to study biological membranes. The term "liposomes" was introduced in 1968 (Sessa and Weissmann 1968).

Liposomes can be classified

(i) according to lamellarity and size (Perez-Soler 1989): Unilamellar vesicles comprising one lipid bilayer have diameters of 50 to 250 nm. They contain a large aqueous core and are eligible for the encapsulation of water-soluble drugs. Multilamellar vesicles composed of several concentric lipid bilayers in an onion-skin arrangement have diameters of 1 to 5 μm. The high lipid content allows these multilamellar vesicles to entrap lipid-soluble drugs passively.

(ii) according to a phylogenetic scheme: Classical or conventional liposomes (ie, simple mixtures of phospholipids and cholesterol) target the reticulo-endothelial system (RES) and are called "RES-targeted liposomes". Vesicle size in liposomes of similar lipid composition is usually inversely correlated with the amount of RES uptake (Senior and Gregoriadis 1982).

Liposomal formulations aim reduce the toxic side effects of conventional cytostatic drugs without hampering the efficacy. Theoretically, these goals may be reached in two ways: (i) the encapsulated drug is prevented from reaching healthy tissue ("site avoidance") and/or (ii) drug concentrations are delivered mainly to neoplastic tissue ("drug targeting").

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Meanwhile, several liposomal formulations have been approved for the treatment of different tumors and have become an established addition to the anti-cancer drug armamentarium (Hofheinz et al 2005).

In this review we briefly summarize the results of liposomal encapsulated cytarabine for the treatment of lymphomatous and leukemic meningitis.

The clinical challenge: lymphomatous and leukemic meningitis

Neoplastic meningitis is characterized by the infiltration of cancer cells into the leptomeninges and associated with a poor prognosis. About 40% to 90% of the patients with neoplastic meningitis suffer from neurological symptoms (DeAngelis 1998; Chamberlain 2005). More sensitive methods such as flow cytometry indicate that central nervous system (CNS) involvement in patients with non-Hodgkin's lymphoma (NHL) or leukemia has been underestimated so far. A recently reported series using flow cytometry detected positive cerebrospinal fluid in 73% of patients (Bromberg et al 2007). Generally, the treatment of neoplastic meningitis is palliative and the goal is prolongation of survival, reduction of neurological symptoms, and improvement of qualitiy of life. The treatment of disseminated lymphomatous meningitis, which may compromise up to 25% of high-grade lymphoma patients, requires a long exposure of the malignant cells to a high concentration of antineoplastic agent to achieve a sufficiently cytostatic effect (Bleyer 1999). As only a few cyctotoxic drugs pass through the blood–brain barrier, effective levels cannot be achieved by systemic chemotherapy alone (Benesch and Urban 2008). Therefore, frequent intrathecal injection of chemotherapeutic drugs either by lumbar punctures or via ventricular access devices has become the mainstay of therapy to achieve effective levels of chemotherapeutic agents in the cerebrospinal fluid (CSF). The antimetabolites methotrexate (MTX) and cytarabine (Ara-C) are agents of choice for intrathecal chemotherapy. Given the low proliferation index of malignant cells in the CNS, their susceptibility to antimetabolite treatment is theoretically increased by longer exposure (Bleyer 1999). The removal of MTX or Ara-C from the CSF is slow, which gives the rationale for the intrathecal use of these drugs.

Until recently, the application of MTX has been preferred to Ara-C for its even lower CSF clearance and deeper penetration into the meninges and CNS parenchyma (Bleyer 1999). Ara-C – a cornerstone in the treatment of hematologic malignancies (Johnson 2001) – requires metabolic activation by the enzyme cytidine deaminase to exert its cytotoxic properties. Within the CSF the activity of cytidine deaminase is low and metabolization almost negligible (Zimm et al 1984). As the terminal half-life of Ara-C in the CSF is only 3.4 hours, 2 to 3 intrathecal applications per week are required to achieve adequate cytotoxic drug concentration over time (Benesch and Urban 2008).

Treatment results with liposomal encapsulated cytarabine

Liposomal encapsulated cytarabine (DepoCyte®, Mundipharma GmbH, Limburg/Lahn, Germany) is an intrathecal injectable suspension of Ara-C encapsulated in multivesicular lipid based particles. Multivesicular liposomes are structurally distinct from lamellar liposomes. They consist of numerous non-concentric water-filled polyhedral compartments separated by bilayered liquid septa (called DepoFoam®-technology) (Angst and Drover 2006). These particles have a diameter of approximately 3 to 30 μm consisting of hundreds of aqueous chambers in a honeycomb arrangement containing Ara-C. The chambers are separated from each other by lipid bilayers consisting of dioleyl-phosphatidycholine, dipalmitoyl-phosphatidylglycerol, cholesterol, and triolein. DepoFoam® particles are therefore much larger than conventional uni- or multilamellar liposomes bearing a high drug-loading capacity. At storage temperatures of 2 to 8 °C the particles are stable for 12 months. After inthrathecal injection the biodegradation of the lipid membranes at body temperature leads to a gradual release of Ara-C ensuring prolonged cytotoxic drug concentrations of cytarabine in cerebrospinal fluid. The lipid compounds enter the normal lipid metabolism pathways. DepoCyte® has a mean half-life of 130 to 277 hours compared with 3 to 4 hours for conventional Ara-C (Zimm et al 1984). In a preclinical study even 16 days after injection the free-drug concentration was higher than the minimal cytotoxic concentration (Kim et al 1987). No Ara-C was found in blood plasma after intrathecal administration of 50 mg of DepoCyte®.

Most of the clinical data published thus far are derived from clinical trials or larger case series (Goekbuget et al 2005; Björgvinsdóttir et al 2006; Camera et al 2006; Cascavilla et al 2006; Garcia-Marco et al 2006; Rossi et al 2006; Sancho et al 2006a, b, 2007; Shapiro et al 2006; Aichberger et al 2007; Brion et al 2007). Few reports deal with the prophylactic use of DepoCyte® (Anaclerico et al 2006; McClune et al 2007; Neumeister et al 2007).

For induction therapy a biweekly dosing schedule of 50 mg DepoCyte® has been established (consolidation and maintainance therapy in 4-weekly intervals). Using this schedule, cytotoxic CSF levels of Ara-C were found up to 14 days regardless of the site of drug injection (ventricular or lumbar) (Kim et al 1993).

One randomized trial was conducted in patients with lymphomatous meningitis. This phase III study compared intrathecal liposomal Ara-C with conventional (free) intrathecal Ara-C in 28 patients with lymphomatous meningitis (Glantz et al 1999b). The experimental treatment arm consisted of biweekly 50 mg DepoCyte® and the reference treatment was Ara-C 50 mg twice weekly for a 1-month induction period. In case of response (CSF clearing of lymphoblasts) consolidation and maintainance cycles with longer application intervals were added. Response rates (ie, clearing of CSF and absence of neurological progression) were statistically significant higher in the DepoCyte® arm (71% versus 15%; $p = 0.006$). Moreover, a strong trend in favor of DepoCyte® in terms of time to neurological progression (78 versus 42 days; $p > 0.5$) and overall survival (99 versus 63 days; $p > 0.5$) was observed. DepoCyte® treatment was associated with an improvement of Karnofsky status at the end of the induction treatment ($p = 0.041$). Consequently, the study was stopped before the initially planned sample size was achieved. The main side effects of both treatments arms were headache and arachnoiditis. Consistent with the higher CSF levels of Ara-C in the DepoCyte® group, headache (grades 1–3) ocurred in a higher amount of treatment cycles (27% versus 2%). Arachnoiditis (grades 1–3) was reported to occur in 22% of DepoCyte® cycles (13% with Ara-C). To prevent or mitigate this adverse event, concomitant oral dexamethasone treatment (4 mg bid days 1–5) is recommended.

Another randomized trial compared biweekly DepoCyte® 50 mg (up to 6 applications) with inthrathecal MTX 10 mg twice weekly (up to 16 applications) in patients with cytologically proven neoplastic meningitis deriving from solid tumors (Glantz et al 1999a). A total of 61 patients were accrued to receive the drugs either via lumbar puncture or an intraventricular Ommaya reservoir. Responses occurred in 26% of patients in the DepoCyte® and 20% in the MTX group. Median survival was not significantly different (105 days with DepoCyte® versus 78 days with MTX), but a longer median time to neurological progression was obtained with DepoCyte® (58 versus 30 days; $p = 0.007$). The grades and extent of adverse events observed were comparable between both groups.

Meanwhile, several phase II studies or larger case series with DepoCyte® in patients with lymphomatous or leukemic meningitis have been reported, and similarly to the data published by Glantz et al response rates in the range of 50% to 70% were noted (for overview see Benesch and Urban 2008).

In the prophylactic treatment setting a prospective clinical trial using DepoCyte® as CNS prophylaxis was recently published (Jabbour et al 2007). Thirty-three patients with previously untreated acute lymphoblastic leukemia or lymphoma received liposomal cytarabine concurrently to systemic chemotherapy. None of the patients treated with DepoCyte® developed isolated CNS relapse. Serious neurotoxicity occurred in five patients within 14 days from the last intrathecal therapy (seizure n = 1, encephalitis n = 1, cauda equina syndrome n = 2, pseudotumor cerebri n = 1). The authors concluded that prior administration of cytotoxic drugs passing the blood – brain barrier such as high-dose MTX or cytarabine might have increased the risk of neurotoxicity. Similar observations have been made by other groups as well, eg, in pediatric patients (Benesch et al 2007). Admittedly, it is difficult to distinguish symptoms by infiltration of CNS from side effects observed after administration of any substance available for intrathecal use alone or in combination with systemic chemotherapy (Weiss et al 1974; Resar et al 1991; Schiller et al 1992; Benesch and Urban 2008). Nevertheless, these observations have led to a discussion among clinicians about the safety of DepoCyte® (Chamberlain and Glantz 2007; Pui 2007).

Concluding remarks

DepoCyte® has consistently shown high response rates in the treatment of patients with lymphomatous and leukemic meningitis in a randomized clinical trial as well as in several case series or phase II studies. Moreover, in this randomized trial the superiority over conventional Ara-C with respect to the improvement of neurological sympstoms was demonstrated. DepoCyte® is approved in the US and in Europe for the intrathecal treatment of lymphomatous meningitis. Owing to the scarcity of this disease, it is expected that further randomized clinical trials for the treatment of malignant leukemic or lymphomatous meningitis will not be conducted and that the question of whether DepoCyte® is truly superior to conventional cytostatics in the intrathecal treatment will remain unresolved. Nonetheless, the mode of administration favors DepoCyte®. Moreover, cost-utility analysis indicates that DepoCyte® is cost-effective (Moeremans et al 2004). In view of the recently reported neurological

toxicities, the use of DepoCyte® as prophylactic treatment, eg, for acute lymphatic leukemia, should remain reserved to clinical trials.

Further open questions are the optimal treatment duration after the initial clearing of CSF from malignant cells, the best dosing regimen for consolidation therapy, and the interval between the administration of DepoCyte® and other potential neurotoxic cytostatic drugs, especially high dose methotrexate or Ara-C (Pui 2007). Finally, the potential benefit of DepoCyte® treatment in malignant meningitis of solid tumors remains a challenge to be explored in further clinical trials.

Disclosures

The author have no conflicts of interest to disclose.

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