Liposomal cytarabine in central nervous system disease of haematological malignancies: more effective but more toxic?

Mar Tormo Díaz

Infiltration of the central nervous system (CNS) is a serious complication in patients with haematological malignancies and is associated with a poor prognosis. CNS involvement in patients with acute lymphoblastic leukaemia (ALL) at the time of presentation is uncommon and has been reported in 5–7% of patients [1]. Without prophylaxis, CNS recurrence occurs in approximately 30% of adult patients and up to 75% of children with ALL in complete response [2, 3]. However, with therapies that incorporate CNS prophylaxis, 5-year event-free survival rates of approximately 80% and 50% have been achieved in paediatric and adult ALL, respectively [4]. In patients with lymphoma, histologic subtype is one of the main risk factors for CNS recurrence. There is consensus on the need for CNS-directed therapy in aggressive lymphomas such as Burkitt's lymphoma and lymphoblastic lymphoma, which have a risk of recurrence, in the absence of prophylaxis, of up to 20–25%. However, there is controversy regarding this therapy for other aggressive lymphomas, such as mantle cell lymphoma, anaplastic lymphoma, peripheral T lymphomas and especially diffuse large B-cell lymphomas. Several studies have estimated the risk of CNS recurrence as about 5%.

The treatment of disseminated lymphomatous meningitis requires long exposure of the malignant cells to a high concentration of antineoplastic agent to achieve a sufficiently cytostatic effect. CNS-directed therapy is based on the administration of high-dose systemic chemotherapy with drugs that can pass through the blood-brain barrier, such as methotrexate (MTX) and cytarabine, cranial or craniospinal irradiation, and intrathecal (IT) administration of MTX and/or cytarabine [5]. Systemic chemotherapy alone is not adequate for CNS prophylaxis and treatment, since it is difficult to maintain prolonged therapeutic concentrations of drugs in the cerebrospinal fluid (CSF).

Moreover, radiation can be effective but is often related to late adverse effects, like secondary neoplasms, neurocognitive dysfunction and neurotoxicity [6]. IT chemotherapy is a standard treatment for lymphomatous meningitis, but only few drugs can be used in this way. In general, treatments use IT MTX, cytarabine or thiotepa. The main problem with these drugs is their rapid clearance from the CSF, meaning 2–3 administrations per week are required, either by lumbar puncture or an implanted Omayra reservoir. This is inconvenient for patients, presents multiple opportunities for injection-related trauma or infection and is a very stressful process for patients and their carers.

Recently, a liposomal formulation of cytarabine (DepoCyt[®], Mundipharma Pharmaceuticals SL, Cambridge, UK) has been developed that has a significantly longer CSF half-life. After administration of a 50-mg injection, free cytarabine is detectable for up to 14 days. The prolonged activity allows better distribution of the drug in the whole CSF surrounding the brain [7]. Liposomal cytarabine has allowed the frequency of administration to be reduced to once every 2 weeks during the induction and consolidation phases, and once every 4 weeks during the maintenance phase. All patients being treated with liposomal cytarabine should receive concomitant oral or IT dexamethasone for five days to reduce the risk of chemical arachnoiditis.

The efficacy and tolerability of IT liposomal cytarabine have been demonstrated in two randomised controlled trials developed in patients with neoplastic meningitis associated with lymphoma [8] and solid tumours [9], although a survival advantage was not demonstrated in the latter study. Based on its significant efficacy, the drug was approved by the Food and Drug Administration and EMEA for the treatment of adults with lymphomatous meningitis. There is less evidence on the use of liposomal cytarabine in children and the recommended dose in a phase I study in patients aged between 3 and 21 years with haematological malignancies or solid tumours was 35 mg [10].

There are concerns about the toxicity associated with liposomal cytarabine, especially when they are used concomitantly with other drugs that cross the blood-brain barrier. The M.D. Anderson experience in adults diagnosed with ALL and treated with a hyper-CVAD regimen that

M. Tormo Díaz (✉)
Hematology and Oncology Service
Clinic University Hospital and INCLIVA Health Research Institute
Av. Blasco Ibáñez 17
ES-46010 Valencia, Spain
e-mail: tormo_mar@gva.es

included high-dose MTX and cytarabine, and the substitution of conventional prophylactic IT treatment with liposomal cytarabine, was associated with a high percentage of neurotoxicity (16%) including encephalopathy, cauda equina syndrome, seizure and pseudotumour cerebri. This toxicity occurred despite having separated the administration of liposomal cytarabine from cytarabine administered systemically by 12 days [11]. They conclude that severe neurotoxicity may occur after concurrent administration of IT liposomal cytarabine and systemic chemotherapy agents that penetrate the blood-brain barrier. Radiation therapy may also potentiate the neurotoxicity associated with liposomal cytarabine. In the randomised trials from Glantz et al., most adverse events were transient and resolved by the end of the treatment cycle in which they occurred. The only adverse event that happened in more than 10% of treatment cycles was headache, which was more frequent in the liposomal cytarabine arm than in the free cytarabine arm (27% vs. 2% of cycles). However, grade 3 headache occurred over only 5% of the liposomal cytarabine cycles. The other common side effect was arachnoiditis, which occurred in 22% of cases of patients treated with liposomal cytarabine vs. 13% of patients treated with free cytarabine. There were no significant differences in episodes of severe arachnoiditis between the two treatment arms. We must take into account in this study that concurrent systemic chemotherapy for treatment of disease outside of the meninges was permitted with the exception of high-dose MTX, cytarabine or thiopeta, which may explain the favourable toxicity profile [8].

Recently, one study has reported the results of a prospective non-randomised multicentre phase II trial for the treatment of CNS relapse in adult patients with ALL and Burkitt's lymphomas with liposomal cytarabine [12]. This study involved a negative group of heavily pretreated patients with ALL and very aggressive lymphoma; the overall rate of CNS cytological response was 74%. On the other hand, 89% patients experienced an adverse event of some degree, of which 68% were grade 3 or 4 and 32% related to liposomal cytarabine.

The article published in this issue by Navajas et al. shows the results of treatment with liposomal cytarabine in a group of paediatric patients from nine Spanish centres with primary CNS tumours and leptomeningeal involvement. Overall, the results were good, with a response rate of 58%, and although 55% of patients experienced side effects, these were mild or moderate. None of these patients received high doses of drugs that cross the blood brain-barrier and only two received concurrent radiotherapy [13].

In conclusion, cytarabine liposome is effective in the treatment of meningitis lymphomatous of ALL, aggressive lymphomas and probably in brain tumours with leptomeningeal involvement. However, additional studies should be conducted in these patients to establish how to use this agent in combination with systemic chemotherapy, especially with drugs that penetrate the blood-brain barrier. Prospective trials are necessary to define the optimal schedule, frequency and combination with systemic therapy.

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