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SPECIAL ARTICLE

Liposomal cytarabine for the treatment of leptomeningeal dissemination of central nervous system tumours in children and adolescents☆

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Abstract Leptomeningeal dissemination in paediatric central nervous system (CNS) tumours is associated with a poor outcome, and new therapeutic strategies are desperately needed. One of the main difficulties in the treatment of CNS tumours is blood brain barrier penetration. Intrathecal therapy has shown to be effective in several paediatric tumours. The aim of this article is to review the data available on the use of liposomal cytarabine for paediatric patients with leptomeningeal dissemination of CNS tumours, including the pharmacology, administration, safety and efficacy data.

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PALABRAS CLAVE
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Citarabina liposomal para el tratamiento de la diseminación leptomeníngea en tumores del sistema nervioso central en niños y adolescentes

Resumen Los tumores pediátricos del sistema nervioso central (SNC) con diseminación leptomeníngea tienen mal pronóstico y es preciso encontrar nuevas alternativas terapéuticas. Una de las principales dificultades en el tratamiento de los tumores del SNC es la penetración de la barrera hematoencefálica, por lo que el tratamiento intratecal ha demostrado su eficacia en múltiples tumores pediátricos. En este artículo se revisa la experiencia disponible sobre la utilización de citarabina liposomal para pacientes pediátricos con tumores del SNC con diseminación leptomeníngea: farmacología, forma de administración, datos de seguridad y estudios de eficacia.

Introduction

Definition and aetiology

The meninges are the most frequent site of metastatic spread in paediatric central nervous system (CNS) tumours. This dissemination can be present at initial diagnosis or persist as minimal residual disease despite initial treatment and recur as metastatic disease.[1] Another explanation for the phenomenon of persistent minimal residual disease and leptomeningeal metastatic recurrence is the presence of the blood–brain barrier (BBB), which blocks the delivery of drugs that are administered systemically.[2]

Diagnosis

Dissemination is suspected based on clinical symptoms and confirmed by abnormal MRI findings or the presence of cancerous cells in cerebrospinal fluid (CSF). The most frequent symptoms are headache, cranial nerve palsy, back pain or radiculalgia. Other possible manifestations include impaired CSF flow or reabsorption with secondary hydrocephalus. Diagnostic MRI findings can have a linear, nodular or mixed enhancement pattern. The diffuse pattern shows contrast uptake or thickening along the margins of the meninges, which can reach nerve root exits in the spinal region.[3] Magnetic resonance abnormalities may be accompanied by the detection of malignant cells in CSF cytology, although in embryonal tumours it is possible to find evidence of dissemination in CSF cytology in the absence of abnormal MRI findings. The usefulness of flow cytometry of CSF samples from paediatric brain tumours has yet to be determined.

Incidence of metastatic dissemination in different types of paediatric tumours

The highest incidence corresponds to embryonal tumours.[4] In medulloblastoma, the most frequent type of malignant CSN tumour in the paediatric age group, the incidence of metastasis at the time of diagnosis ranges between 20% and 30%. Thirty percent of medulloblastomas do recur, usually with leptomeningeal dissemination. Metastatic disease becoming resistant to multimodal therapy is the usual cause of death in these patients, as opposed to local recurrence. The incidence of metastasis is particularly high in group 3, followed by group 4 and the Sonic Hedgehog medulloblastoma subgroups.[5] In other embryonal tumours, such as the supratentorial primitive neuroectodermal tumours (PNET), which include pineoblastoma, embryonal tumours with multilayered rosettes (ETMRT), and atypical teratoid-rhabdoid tumours (ATRTs), dissemination may be found at the time of diagnosis or in a subsequent recurrence.

The incidence of dissemination is lower in gliomas.[6,7] Recent studies on diffuse intrinsic pontine glioma revealed that up to 38% of patients had leptomeningeal spread at autopsy.[8] A study on ependymoma reported that 9–20% of patients had dissemination at diagnosis, with a higher incidence in recurrent cases.[9] Dissemination is rarely found in glioneural tumours, such as ganglioglioma or dysembryoplastic neuroectodermal tumour, but is a consistent finding in the rare cases of disseminated glioneural tumour.[10] The incidence of dissemination in malignant germ cell tumours (germinomas, secretory germ cell tumours and mixed germ cell tumours) ranges between 10% and 20% at the time of diagnosis.[11]

The probability of developing CNS metastases from extracranial tumours is much lower in children and adolescents than in adults. The most frequent tumours with CNS metastases are sarcoma (Ewing sarcoma, osteosarcoma, synovial sarcoma), neuroblastoma, Wilms tumour and retinoblastoma.[12]

Treatment options

The goal of treatment for leptomeningeal dissemination can be preventive, when dissemination is not detectable by the usually available methods at initiation, or therapeutic, when there is evidence of metastatic disease in MRI or cytology. The treatment used most commonly is craniospinal irradiation covering the entire neural axis. In combination with chemotherapy, this approach has achieved cure rates in excess of 60% in patients with metastatic medulloblastoma,