Patients with breast cancer that has metastasised to the meninges may now be treated with DepoCyt, a slow-release formulation of the cytotoxic drug, cytarabine.

This treatment has been reported in studies published in October 2000([1]) and January 2001([2]). Both report encouraging therapeutic benefit in combating neoplastic meningitis in breast cancer, but cite arachnoiditis as one of the major adverse effects: 19% in one study, of which 88% were Grade 1 or 2 and

"chemical arachnoiditis (i.e. headaches, fever, nausea, vomiting) was common".

Despite a probably low survival (1 year survival projected as 19%) and the need for fewer injections (about a quarter the number needed in ?conventional' therapy) one must register concern as to the high incidence of arachnoiditis and the potential longer-term effects for those survivors.

In May 2002, doctors from Florida published a paper ([3]) on an open label trial of DepoCyt for the intrathecal treatment of solid tumour neoplastic meningitis.

They found that grade 3 or 4 arachnoiditis occurred on 6% of treatment cycles, and reported:

"The most important adverse events were headache and arachnoiditis."

METHOTREXATE:

Whilst MTX is clearly an important drug in the management of serious (rheumatoid arthritis) and sometimes life-threatening conditions (leukaemia, sarcoma), it does carry substantial risks of toxicity, especially to the liver, kidneys and nervous system, which can prove fatal.

Current practice of intense triple chemotherapy has dramatically improved remission and survival rates from Acute Lymphoblastic Leukaemia (ALL), a lethal childhood leukaemia.

Early implementation of central nervous system ?sanctuary therapy' is critical in preventing CNS relapse. Obviously this life-saving treatment is vital, but the risk of arachnoiditis developing later should be borne in mind when assessing longer-term outcomes.

Chronic toxicities include leukoencephalopathy and a range of behavioural, neurophysiological and neuroendocrine disturbances.

Brain et al in 1997, ([4]) in Dijon, France noted that intrathecal methotrexate (MTX) caused cerebral toxicity: acute, subacute and delayed, as well as a chronic delayed leukoencephalopathy if used in conjunction with intravenous MTX and cerebral irradiation.

They cited a case of a 21 year old patient who developed subacute encephalitis and arachnoiditis following administration of intrathecal (i-t) MTX to treat osteosarcoma.

Koh et al, ([5]) in Los Angeles, described "progressive paraplegia" and anterior lumbosacral radiculopathy after i-t MTX.

Lovblad et al described methotrexate encephalopathy with seizures. ([6]) whilst Rubnitz et al ([7]
) quantified the risk of transient focal neurological deficits in children with ALL given intravenous and intrathecal methotrexate as around 3%.

A Finnish group ([8]) noted that "Chemical arachnoiditis is known to be associated with

intrathecal methotrexate therapy in children with leukaemia."

They were looking at collagen in the spinal fluid, which can be affected in ALL.

The authors noted that there is a fibroproliferative response to inflammation in the arachnoid which is related to concentrations of a certain type of procollagen.

They postulated that administration of steroids may help to reduce this response and prevent development of adhesions in the arachnoid.

A Dutch group ([9]) later looked at cells in the spinal fluid; they found an increase in protein levels in the CSF and increased cell numbers which they attributed to arachnoiditis due to MTX therapy a few days earlier.

Further adverse effects were noted in the Indian Journal of Radiology and Imaging ([10]): "paresis, paraplegia and chemical arachnoiditis".

Intrathecal treatment is also used for central nervous system prophylaxis in Non-Hodgkin's lymphoma.

CONCLUSION:

As Staats et al, in 1999 ([11]) described,

"Spinal cord or nerve root toxicity may manifest itself as histologic, physiologic, or behavioural/clinical derangements after exposure to a spinal drug."

They maintain that

"the neurotoxicity of spinal drugs is a central safety issue. ...we hope that this review stimulates future research on spinal drugs to follow a systematic approach to determining potential neurotoxicity."

In England, Jolles, Sewell and Leighton, at the National Institute for Medical Research, published a paper on

"Drug-induced aseptic meningitis (DIAM): diagnosis and management" ([12])

and noted that intrathecal agents were (unsurprisingly) in the major categories of causative agents.

They also remarked that

"there appears to be an association between DIAM and connective tissue disease, particularly systemic lupus erythematosus, and ibuprofen."

It is worth noting also that many patients who have rheumatoid arthritis may thus be at higher risk of developing chemical meningitis and possibly the chronic sequela of arachnoiditis, if intrathecal drugs are administered.

Hodgson et al., in their 1999 paper ([13]), conclude:

"Overall, most spinal drugs in clinical use have been poorly studied for spinal cord and nerve root toxicity."

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