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Cognitive functioning following chemotherapy : a study in breast cancer patients

Schagen, S.B.

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Chapter 3

Neurotoxicity of agents under study

Adverse effects of adjuvant chemotherapy

Adjuvant chemotherapy is administered to prolong disease-free and overall survival of patients with operable breast cancer. Unfortunately, the treatment regimens involved in adjuvant chemotherapy may be associated with both short- and long-term toxicities.

In this chapter, the major neurological toxicities of the chemotherapeutic agents used in the adjuvant treatment of the breast cancer patients participating in the neuropsychological studies are reviewed. Three regimens are relevant in this respect:

- CTC regimen: cyclophosphamide, 6 g/m² intravenously; thiotepa, 480 mg/m² intravenously; carboplatin, 1.6 g/m² intravenously, divided over four days
- FEC regimen: 5-fluorouracil, 500 mg/m² intravenously; epidoxorubicin, 90-120 mg/m² intravenously; cyclophosphamide, 500 mg/m² intravenously, repeated every three weeks
- CMF regimen: cyclophosphamide, 100 mg/m² orally on days 1 to 14; methotrexate 40 mg/m² intravenously on days 1 and 8; 5-fluorouracil 600 mg/m² intravenously on days 1 and 8, repeated every four weeks

The Blood-brain barrier

In principle, the central and peripheral nervous systems are protected against neurotoxic effects of chemotherapeutic agents. The blood-brain barrier is the mechanism assumed to limit entry to the brain of potentially toxic substances and to maintain a constant internal environment, which is of primary importance for optimal neuronal functioning.

The endothelial cells of the brain capillaries form the blood-brain barrier. Its primary characteristic is the permeability of the capillary wall, which is mainly the result of two factors: (1) the restricted para-cellular transport due to the presence of complex tight junctions and (2) the low endocytic activity of the cerebral capillary endothelium. As a consequence, all substances that enter the brain must follow the transcellular route through the endothelial cell. Essential nutrients are delivered to the brain by selective transport mechanisms such as the glucose transporter and a variety of amino acid transporters. Compounds that do not use facilitated or active transport systems can enter only by passive diffusion. As a result, their entry to the brain depends on their molecular weight and their lipophilicity as defined by their octanol: water partition coefficient. Active extrusion by transporters also helps to protect the brain, in particular in case of lipophilic compounds, which might otherwise penetrate the blood-brain barrier relatively efficiently.¹ Results in P-glycoprotein knock out mice clearly show that this transport protein markedly limits the brain penetration and retention of many substrate drugs.² Recent studies demonstrated the importance of MRP1 in the blood-cerebrospinal fluid barrier in the clearance of substrate drugs from the central nervous system

and it is obvious that many other transporters may be involved in the uptake or efflux of drugs over the blood-brain barrier.^{3,4}

Agents under study

Cyclophosphamide

Cyclophosphamide is the most frequently used alkylating agent. Alkylating agents act by transferring alkyl groups onto amino acid residues of cellular proteins, resulting in covalent bond formation with cellular molecules. It is the reaction of the drug with the DNA that determines the cytotoxic effect. Alkylating agents form crosslinks with DNA, preventing transcription and replication of DNA.⁵

A unique toxicity of cyclophosphamide is hemorrhagic cystitis due to irritation of the bladder mucosa from urinary metabolites. The most important dose-limiting toxicity of cyclophosphamide (other than bone marrow depression) is cardiac toxicity. Cyclophosphamide does not cross the blood-brain barrier easily, and CNS toxicity is seldom observed. Encephalopathy occurs in few instances, but this is probably secondary to the metabolic disturbances caused by inappropriate secretion of antidiuretic hormone (SIADH).⁶

Thiotepa

N,N,N'-triethylenethiophosphoramidate (thiotepa) is also an alkylating agent, and its cytotoxicity is thought to be mediated by the formation of DNA interstrand crosslinks. Thiotepa penetrates the CSF. The dose-limiting toxicity of conventional doses of thiotepa is myelosuppression⁷, whereas in very high-doses central nervous system toxicity (acute encephalopathy) has been reported.⁸

Carboplatin

Carboplatin is a second generation platinum-containing compound. The mode of action of both cisplatin and carboplatin is the formation of DNA crosslinks, in a manner similar to that of alkylating agents.⁵

The dose-limiting factor of carboplatin is myelosuppression. Given as high-dose single agent treatment, the principal non-hematological toxicity is renal toxicity. Ototoxicity with high-frequency hearing loss may occur after carboplatin treatment, but this is less common than after cisplatin therapy. Carboplatin causes mild peripheral neuropathy. Following high-dose carboplatin, presence of the drug can be found in ascites, pleural effusions and in the CSF.⁶

5-fluorouracil

5-fluorouracil belongs to the antimetabolites. Antimetabolites interfere with the normal metabolism of RNA or DNA precursors because of their structural similarity to intermediates in the synthetic pathway. These structural analogues interfere with the action of a key enzyme

in the synthetic process. Specifically, 5-FU blocks DNA synthesis by inhibiting the enzyme thymidylate synthase.⁵

5-FU readily enters the CSF. The spectrum of toxicities associated with 5-FU varies considerably depending on the dose, schedule and route of administration, but the most important systemic toxicities are myelosuppression, diarrhea and mucositis. The major neurotoxicity is an acute cerebellar syndrome consisting of slurred speech, ataxia of the trunk or extremities and nystagmus. The incidence is approximately 1% and is dose-dependant; it does not occur with schedules used in FEC or CTC regimens. The cerebellar toxicity is nearly always reversible within some weeks. Cognitive dysfunction is rarely seen and improves after 5-FU discontinuation.⁵

The biochemical basis for 5-FU neurotoxicity is not well understood. It has been postulated that neurotoxicity is due to Krebs's cycle blockade by fluorocitrate, a 5-FU metabolite, but it may be 5-FU itself that causes CNS toxicity.⁶

Epidoxorubicin

Epidoxorubicin is an anthracyclin antibiotic. The anthracyclines are considered to produce their effect by intercalation in DNA, by generating intracellular free radicals and by interacting with the DNA repair enzyme topoisomerase II.⁵

Anthracyclines as a class are unable to cross the blood-brain barrier either because of low lipophilicity, the presence of P glycoprotein in the cells of the brain endothelial vessels or both. The dose-limiting acute toxicity of the anthracyclines is myelosuppression. Cardiac toxicity is also associated with anthracyclines.¹ Antibiotics at normal systemic dosages are free of neurological complications.⁶

Methotrexate

Methotrexate belongs to the antimetabolites. Its principal mode of action is as a competitive inhibitor of the enzyme dihydrofolate reductase, leading to inhibition of DNA, RNA, and protein synthesis by limiting the availability of reduced folates.

The primary toxic effects of MTX therapy are myelosuppression and gastrointestinal mucositis. It is also associated with both acute and chronic hepatotoxicity. Neurotoxicity is a well-recognized complication, consisting of acute, subacute, or delayed effects. In general, the acute and subacute toxicities are either relatively benign or reversible while the delayed toxicities are more serious and may be irreversible.⁵

MTX seems to have little or no neurotoxicity when used orally or intravenously in conventional doses. High-dose intravenous use is sometimes followed by encephalopathy. The neurologic dysfunction may be acute and transient or delayed in onset with personality changes followed by progressive dementia. It has been postulated that MTX exerts a direct

toxic effect on nerve cells, but also that the toxicity arises from MTX-related impairment of synthesis of neurotransmitters and the accumulation of adenosine and homocysteine, which might contribute to the vascular pathology and ischemic brain injury.⁶

When the drug is administered intrathecally, it can cause chemical meningitis, but this is uncommon. A progressive leukoencephalopathy may also follow intrathecal MTX. The neurotoxic effect is related with high drug levels and high cumulative concentrations in the CSF.⁶

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