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ScienceDirect
Cancer Letters 267 (2008) 1–9
CANCER Letters
www.elsevier.com/locate/canlet

Mini-review

Anticancer drugs and central nervous system: Clinical issues for patients and physicians

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Received 21 November 2007; received in revised form 21 February 2008; accepted 22 February 2008

Abstract

Anticancer drugs may cause neurological toxicity involving the central nervous system. Patients receiving anticancer treatment may develop encephalopathy, extrapyramidal reactions, seizures, cerebellar dysfunction, retinopathy, cerebral venous thrombosis, myelopathy, cognitive impairment, and psychiatric symptoms. Physician should carefully evaluate neurological signs and symptoms in order to recognize these drug-related adverse reactions.

In this review we aimed at presenting different neurological complications of anticancer drugs and their management. PUBMED search was performed in order to retrieve all articles and case reports dealing with central nervous system toxicity related to anticancer treatments.

Keywords: Anticancer drugs; Central nervous system; Encephalopathy; Neurological toxicity

1. Introduction

Cancer patients receiving chemotherapy, endocrine therapy, or immunotherapy may develop central nervous system (CNS) disorders. Besides of drug-related adverse events, disorders of the CNS may be the consequence of the direct involvement by the tumour (cerebral and meningeal metastasis) or be part of the clinical picture of paraneoplastic syndromes. Whole brain radiotherapy may also cause CNS toxicity with cognitive deterioration, cortical atrophy, and leukoencephalopathy.

Different areas of the CNS may be affected presenting with different clinical symptoms and signs. A multidisciplinary approach, with the collaboration of the oncologist and the neurologist could improve the management of these adverse effects.

In this review, we will focus on CNS disorders related to anticancer drugs that include: encephalopathy; extrapyramidal reactions; seizures; cerebellar dysfunction; retinopathy; cerebral venous thrombosis; myelopathy; cognitive impairment; psychiatric symptoms.

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doi:10.1016/j.canlet.2008.02.051

2. The blood–brain barrier

The exchanges of fluids and molecules among the different compartments of CNS are highly selective and they occur in response to osmotic and hydrostatic forces, representing a sort of barrier.

The blood–brain barrier (BBB) is both a functional and an anatomical barrier.

Its existence was demonstrated for the first time in late 19th century by Ehrlich [1], who reported that i.v. injections of albumin-bound dye into rats stained all the tissues, but not the brain.

The endothelial cells of cerebral capillaries are the anatomical substrate of BBB: they differ from those of peripheral capillaries because they are not fenestrated and contain few endocytotic vesicles. They make contact with each others through tight-junctions that further limit intercellular fluxes. The permeability of BBB reflects the tightness of these junctions, which is somehow regulated by factors secreted by pericytes and astrocytes, whose processes form end-feet that surround brain microvessel.

The molecular constituents of brain endothelial tight-junctions have been recently elucidated: they consist of transmembrane and intracellular proteins [2]. Transmembrane proteins include the family of claudin, occludin, and junctional adhesion molecule (JAM). Occludin is expressed ubiquitously in tight-junctions, while claudins are tissue-specific; in fact, brain endothelial cells express claudin-1 and cludin-5 [3]. Another family of proteins involved in the structure of BBB is represented by aquaporins (AQPs). They are water channels proteins that provide a major pathway for osmotically-driven water flows across plasma membrane, in different types of cells.

In the brain, AQP4 is the major water channel, strongly expressed in astrocyte plasma membrane, including pericapillary foot processes. This localization suggests its involvement in fluid transport in and out of the brain, thus participating to the structure of BBB [4].

Despite the presence of BBB, CNS toxicity occurs, especially when the BBB is injured, overwhelmed by high systemic doses of chemotherapy or bypassed with intrathecal administration of drugs.

Primary brain tumours (PBTs) and brain metastases induce leak of BBB by promoting angiogenesis and causing defects in inter-endothelial cells tight-junctions. Moreover, endothelial cells exhibit the characteristics of peripheral vessels, such as fenestrations and expressions of peripheral molecular markers. It has been suggested that those changes in brain micro-vessels represent the response to signals and angiogenic growth factors produced by surrounding tumour cells [5] in presence of reduced number of normal astrocytes, resulting in lack of astrocyte-derived factors required for the building up of a normal BBB.

Recently, constitutional elements of tight-junctions such as occludin and claudins have been demonstrated to be down-regulated and phoshorylated in human gliomas, and even absent in brain metastases [6]. On the contrary, AQP4 is strongly up-regulated in astrocytes localized in proximity of brain tumours. Unlike normal brain, brain-tumour associated AQP4 are not polarized to astrocyte foot processes: they are expressed throughout the whole astrocyte cells membrane [7] causing an increase in water fluxes through the BBB.

Moreover, tumour-induced alterations in BBB permeability involve also the active transport of lipophilic substances. Transporters known as multidrug resistance (MDR) regulate the penetration of exogenous lipophilic substances in the brain. Many candidate drug-resistance genes have been investigated, such as the adenosine triphosphate (ATP)-binding cassette family (ABC). This family includes the MDR gene 1, which products the glycoprotein P (P-gp) and the members of the MDR-associated proteins (MRPs). The MDR1 is an energy-dependent efflux transporter and protects the brain tissue from toxins and xenobiotics. Up-regulation of MDR1 plays a predominant role in tumour as well as in epilepsy pharmacoresistance [8].

Chemotherapy-induced neurotoxicity, indeed, can be enhanced by pathological changes in BBB due to neoplasms or other treatments (e.g. radiotherapy), and depends on drugs pharmacokinetics and pharmacodynamics and on the route of administration.

Radiotherapy may affect the BBB directly or indirectly. Ionizing radiations cause a direct lesion to glial cells, both oligodendrocytes and astrocytes, leading to demyelinization of white matter and loss of astrocytes' specialized functions in BBB. Moreover, the microcirculation, which is an anatomical component of BBB, is affected by radiotherapy, through hyalinized thickening and fibroid necrosis of the vessels [9].

Thus, previous or concomitant radiotherapy represents a cause of additive or even synergistic neuro-