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Pharmacotherapy for adults with tumors of the central nervous system

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ABSTRACT

Tumors of the adult central nervous system are among the most common and most chemoresistant neoplasms. Malignant tumors of the brain and spinal cord collectively account for approximately 1.3% of all cancers and 2.2% of all cancer-related deaths. Novel pharmacological approaches to nervous system tumors are urgently needed. This review presents the current approaches and challenges to successful pharmacotherapy of adults with malignant tumors of the central nervous system and discusses novel approaches aimed at overcoming these challenges.

Contents

1. Introduction

Tumors of the central nervous system (CNS) are both common and therapeutically difficult. They are problematic across the entire age spectrum. The most common malignant tumors of the CNS are derived from glial cells and include oligodendrogliomas, astrocytomas, and glioblastomas (Fig. 1). The American Cancer Society estimates that 21,810 malignant tumors of the brain or spinal cord will be diagnosed during 2008 in the US. Approximately 13,070 people will die from these malignant tumors. This type of cancer accounts for approximately 1.3% of all cancers and 2.2% of all cancer-related deaths (American Cancer Society, 2008).

Clearly, new approaches are critically needed for malignant tumors of the CNS. This review discusses current approaches and challenges to the pharmacotherapy of malignant tumors of the brain and spinal cord in adults and presents novel approaches aimed at overcoming these challenges.

Pharmacoresistance of brain tumors is clearly multifactorial. Brain tumor resistance mechanisms include multidrug resistance factor 1 and P-glycoprotein (MDR1/P-gp), O^6-methylguanine methyltransferase (MGMT), multidrug resistance protein (MRP), metallothioneins, glutathione and glutathione-S-transferases (GSH/GSTs), dihydrofolate reductase (DHFR), protein kinase C (PKC), and topoisomerase-IIα. Aberrant drug transport with MDR1 is bidirectional (decreased influx

Abbreviations: BBB, blood-brain barrier. BCNU, 1,3-bis-(2-chloroethyl)-nitrosourea. BSO, buthionine sulfoximine. CNS, central nervous system. DIABLO, direct inhibitor-of-apoptosis protein-binding protein with low pI. DNA, deoxyribonucleic acid. DHFR, dihydrofolate reductase. EGFR, epidermal growth factor receptor. FADD, fas-associated protein with death domain. G-CSF, granulocyte colony stimulating factor. GH, growth hormone. GSH, reduced glutathione. GST, glutathione-S-transferase. HIF, hypoxia-inducible factor. IAP, inhibitor of apoptosis protein. IGFR, insulin-like growth factor. IL, interleukin. LRP, lung resistance protein. MAPK, MAP kinase. MDR1, multidrug resistance factor 1. MGMT, O^6-methylguanine methyltransferase. MRI, magnetic resonance imaging. MRP, multidrug resistance protein. mTOR, mammalian target of rapamycin. N-CAM, neural cell adhesion molecule. PARP, poly ADP ribose polymerase. PCNA, proliferating cell nuclear antigen. PDGF, platelet-derived growth factor. P-gp, P-glycoprotein. PI3K, phosphatidyl-inositol-3-kinase. PKC, protein kinase C. PTEN, phosphatase and tensin homolog. ROS, reactive oxygen species. RT-PCR, real-time polymerase chain reaction. Smac, second mitochondria-derived activator of caspase. SSTR, somatostatin receptor. TRAIL, TNFα-related apoptosis-inducing ligand. TRP, tyrosine-related peptide. VEGF, vascular endothelial growth factor.

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and increased efflux); with MRP, it is unidirectional (increased efflux only). GSH/GST has been approached in preclinical models using the GSH synthesis inhibitor, buthionine sulfoximine (BSO), and using genetic manipulation of the drug-specific GST isoform. Topoisomerase-IIα is a marker for cell turnover and associated with atypical MDR phenotype. MGMT is suppressed by p53. Metallothioneins inactivate platinum compounds by forming a complex with them. PKC isoforms play three distinct roles in brain tumors: they allow them to arrest in G2 to repair DNA; when overexpressed, they prevent apoptosis; they alter expression of MDR1, P-gp, GST, and MGMT. Altered VEGF expression and alterations in chromosomes 1P and 19q are also implicated in resistance/susceptibility (Bredel and Zentner, 2002; Calatozzolo et al., 2005).

The tumor suppressor p33ING1 has growth-inhibitory and pro-apoptotic effects involving recruitment of p53. p33ING1 also plays a role in DNA repair through interaction with proliferating cell nuclear antigen (PCNA). Various malignant brain tumor cell lines were examined for their sensitivity to cisplatin, doxorubicin, etoposide and the antimitotic agents vincristine and paclitaxel. In general, ING1 levels were higher in glioma cell lines than in normal control cells. Comparing glioma cell lines, p33ING1 gene expression correlated significantly ($p=0.028$) with resistance to vincristine ($r^2=0.87$; Tallen, Riabowol, & Wolff, 2003). Higher glioblastoma cell plating density in vitro results in higher resistance to chemotherapeutic drugs. This suggests that there are autocrine or paracrine factors that facilitate resistance (Ng, Wan, & Too, 2007).

For many years, blood-brain barrier (BBB) penetration was the single most important obstacle facing chemotherapy for brain tumors. Significant progress has now been made in this regard (Gururangan & Friedman, 2002). The hypothesis has been advanced that tumor hypoxia mediates and perpetuates the transformation of more benign tumors to more malignant ones by selecting those cells for survival that express hypoxia-tolerant proteins [e.g., hypoxia-inducible factor (HIF)] and that enhance angiogenesis (Jensen, 2006).

The role of steroids in modulating BBB and chemoresistance of brain tumors is controversial. Steroids modulate P-gp function, are a P-gp substrate, and decrease chemotherapeutic agent uptake into the CNS. However, dexamethasone has also been reported to induce chemoresistance in brain tumor cells (Zhang et al., 2006).

Often, drug concentrations are higher in tumor than in surrounding normal tissue, implying a more permeable BBB in the former, and leading to the concept of the blood-tumor barrier. The BBB has been defined on anatomic, molecular, and electrophysical bases. No one of these alone accounts completely for the behavior of the BBB relative to uptake and distribution of chemotherapeutic agents into the CNS. There are apparently at least two drug binding sites on P-gp; one binds drugs that inhibit transport via the other site, but does not transport them. The other binds and transports drugs. Knowing to which site a drug binds helps determine its effect on chemotherapeutic resistance. It is not clear what the role of other resistance proteins (e.g., MRPs) is in chemoresistant primary brain tumors. Attempts to open up the BBB to let drugs in include osmotic methods (intraarterial mannitol) and bradykinin analogue administration (raising intracellular Ca^{++} and thereby opening tight junctions). Early human trials of the latter gave mixed results. Use of verapamil or cyclosporine or analogues to circumvent P-gp has proven to be disappointing in CNS tumors in vivo. Irradiation seems to decrease P-gp expression and seems to work synergistically with P-gp inhibitors. Adjunctive, simultaneous irradiation and chemotherapy may be useful for this reason (Bart, Groen, Hendrikse, van der Graaf, Vaalburg, & de Vries, 2000).

In addition to attempts to overcome chemoresistance, brain tumor research has been aimed at designing novel methods for predicting for a given tumor which available therapies are most likely to be effective and which are most likely to meet resistance. Diffusion imaging and, more recently, sodium MRI have demonstrated their distinct abilities to detect therapy-induced alterations in tumor cellularity, which has been demonstrated to be indicative of therapeutic efficacy. More importantly, both imaging modalities detect tumor response much earlier than traditional methodologies that rely on macroscopic volumetric changes (Schepkin et al., 2006). Proteomics holds the promise of allowing a molecular understanding of the resistance of CNS tumors to chemotherapy and individualization of therapy (Valera, Machado, Scrideli, Lucio-Eterovic, & Tone, 2007; Valera, Lucio-Eterovic, et al., 2007). The potential already exists to use microarray and informatics technology to discern patterns of gene expression associated with chemoresistance and to discover novel mechanisms and effectors of such resistance (Bredel et al., 2004).

2. Gliomas and glioblastomas

Glial neoplasms represent 0.5–1% of all cancers in most Western countries. Malignant gliomas are among the most devastating cancers, leading to death in most cases. Techniques to circumvent the resistance mechanisms to chemotherapy in gliomas are being evaluated. Tyrosine kinase inhibitors are among the latest agents to show activity in malignant primary brain tumors. Radioimmunotherapy remains an area of active research (Desjardins et al., 2005). Proposed new strategies for improving therapy for glioblastoma include: temozolomide, an alkylating agent; molecular profiling by microarray and related techniques;

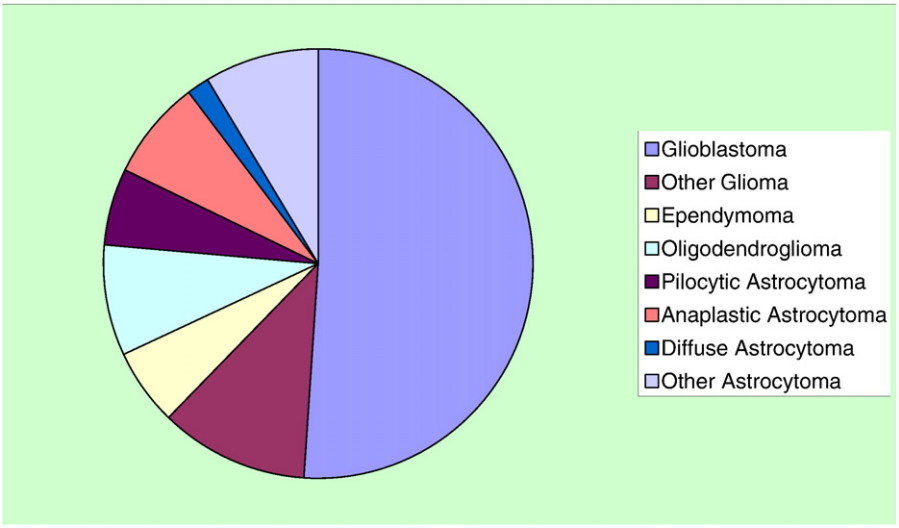

Fig. 1. Fractional incidence of subtypes of nervous system gliomas (Central Brain Tumor Registry of the United States, 2007).