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NEW APPROACHES TO PHARMACOTHERAPY OF TUMORS OF THE NERVOUS SYSTEM DURING CHILDHOOD AND ADOLESCENCE

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Abstract

Tumors of the nervous system are among the most common and most chemoresistant neoplasms of childhood and adolescence. Malignant tumors of the brain collectively account for 21% of all cancers and 24% of all cancer-related deaths in this age group. Neuroblastoma, a peripheral nervous system tumor, is the most common extracranial solid tumor of childhood, and 65% of children with this tumor have only a 10 or 15% chance of living 5 years beyond the time of initial diagnosis. Novel pharmacological approaches to nervous system tumors are urgently needed. This review presents the role of and current challenges to pharmacotherapy of malignant tumors of the nervous system during childhood and adolescence and discusses novel approaches aimed at overcoming these challenges.

Keywords

childhood; adolescence; brain tumors; gliomas; spinal cord tumors; neuroblastoma; cancer chemotherapy

1. Introduction

Collectively, tumors of the brain are the most common solid tumors of childhood. They account for 4.3 cases per 100,000 person years in the U.S. and are among the leading causes of cancer-related morbidity and mortality during childhood (Abdullah et al., 2008; Gottardo and Gajjar, 2008). The most common spinal cord tumors in childhood are ependymomas, neurolemmomas, and astrocytomas (Zhou et al., 2008). These tumors often present with back pain (67%), abnormalities of gait and coordination (42%), spinal deformity (39%), focal weakness (21%), and sphincter disturbance [20%; (Wilne et al., 2007)]. Fig. 1 shows the distribution of central nervous system tumors by anatomic site (A) and by histology (B) in children and adolescents (Central Brain Tumor Registry of the United States, 2008).

Neuroblastoma is by far the most common cancer in infants and the fourth most common type of cancer in children. There are approximately 650 new cases of neuroblastoma each year in the US. The average age at the time of diagnosis with neuroblastoma is about 17 months.

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Around one third of cases are diagnosed by the first year. Nearly 90% of cases are diagnosed by age 5. Only about 2% of cases are found in people over the age of 10, including some adults. In rare cases, neuroblastoma is detected by ultrasound even before birth. In as many as 60 or 70% of cases, the disease is not diagnosed until it has already spread to distant organs. For these latter children, 5-year survival rates with currently available chemotherapy are estimated at between 5 and 20% (Schor, 2002; American Cancer Society, 2008). \

Clearly, new approaches are critically needed for malignant tumors of the nervous system in childhood. This review discusses the role of and challenges to the pharmacotherapy of malignant tumors of the brain and spinal cord and neuroblastoma and presents novel approaches aimed at overcoming these challenges.

2. Brain Tumors

The role of largely empirically-derived, currently available chemotherapy in the treatment of pediatric brain tumors varies by patient age and tumor type, and the application of molecular and cell biological information to further development of such treatment is currently in its infancy (Gottardo and Gajjar, 2008; Pollack, 2008).

Resistance to conventional chemotherapeutic agents appears to contribute to the poor response rate of some childhood brain tumors to chemotherapy. For example, low expression of deoxycytidine kinase by childhood brain tumors renders them poorly responsive to ara-C (Hubeek et al., 2004). MGMT is particularly involved in resistance to alkylating agents like BCNU and temozolomide, the current mainstay of therapy of glioblastoma multiforme in adults. Adjunctive use of O-benzylguanine, an inhibitor of MGMT, overcomes resistance in pediatric brain tumor cells (medulloblastoma, astrocytoma, oligodendroglioma, ependymoma) in culture. However, to overcome chemoresistance, one needs to completely inhibit MGMT both before and for some time after chemotherapeutic agent exposure (Bobola et al., 2005).

Toxicity to the developing brain is a major impediment to the development of effective therapeutic regimens for brain tumors of childhood and adolescence. Cognitive and neuroendocrine sequelae are common and often result in lifelong impairment.

One small study of a group of 18 children with heterogeneous brain tumor types exemplifies the dismal prognosis of these tumors in general. Sequential stem cell-supported high dose cyclophosphamide and carboplatin was tolerable in children with brain tumors and produced responses in children with primitive neuroectodermal tumors (PNETs) and germinomas. There were six complete responses, two partial responses, four children with stable disease, and six children with progressive disease. The median duration of tumor response was 10 months (range: 1.5–87 months), with two children disease-free at 66 and 87 months. Actuarial survival was only 21% (Foreman et al., 2005). That said, chemotherapy has vastly improved the outlook for children with medulloblastoma and has afforded delay of institution of radiation therapy in infants with brain tumors, decreasing somewhat the toxic effects of radiation to the developing brain (Gottardo and Gajjar, 2008).

2.1. Medulloblastoma and PNET

Before the 1980s, therapy for medulloblastoma and other PNETs consisted of surgery and craniospinal radiotherapy. Radiotherapy took an enormous toll on the cognitive function of these developing children and long-term survival rates were still dismal. Two outgrowths of studies done during the 1980s and 1990s vastly changed the outcome for children with medulloblastoma. The first was the stratification of patients and their therapy by risk group based on the absence or presence of drop metastases of the tumor. The second was the addition of chemotherapy to the treatment regimens of both risk groups (Pollack, 2008).

For children with standard-risk medulloblastoma (no metastases), the addition of chemotherapy, most often currently consisting of cisplatin plus etoposide (Akyuz et al., 2008), improved event-free, 5-year survival from 60% to > 80% and afforded reduction in the dose of craniospinal irradiation and, thereby, in the effects on cognition of therapy for medulloblastoma (Karajannis et al., 2008). Medulloblastomas are the most sensitive to etoposide of all neuroepithelial tumors tested. Sensitivity correlates with levels of topoisomerase II α expression (Uesaka et al., 2007).

For children with high-risk medulloblastoma (metastatic disease), chemotherapy is aimed not only at directly killing tumor cells, but also at sensitizing tumor cells to radiation. Event-free, 5-year survival rates for these children have improved somewhat, from < 40% to 60% (Pollack, 2008; Akyuz et al., 2008).

Children with recurrent medulloblastoma present a particularly difficult therapeutic problem. Kadota et al. (2008) have been successful in attaining long-term survival in some children who underwent myeloablative chemotherapy including melphalan and cyclophosphamide followed by bone marrow transplantation.

For medulloblastoma, the future undoubtedly holds targeting of therapy to the particular molecular characteristics of individual patients and tumors. Microarray analysis with subsequent confirmation of altered expression of specific genes has already proven interesting both in determination of prognosis and risk (de Bont et al., 2008) and in discovery of potential targets for novel therapeutic agent development (Pollack, 2008).

2.2. High-grade glioma and glioblastoma multiforme

High-grade gliomas are a heterogeneous group of tumors, the most malignant of which is glioblastoma multiforme. They are difficult to conquer and it is difficult to say definitively what the prognosis for patients with these tumors is. Studies are fraught with heterogeneity of histological diagnosis and, as a consequence, study results are difficult to reproduce and interpret. In fact, it is even difficult to be certain that the addition of chemotherapy changes ultimate outcome relative to treatment with radiation therapy alone (Gottardo and Najjar, 2008).

As is the case for adults with these tumors, temozolomide was tried in children with high-grade gliomas. Five of 8 who received at least 8 cycles of temozolomide had at least a minimal response; none had a complete response (Verschuur et al., 2004). Temozolomide plus cisplatin should be synergistic, as temozolomide prevents DNA repair of damage done by cisplatin. Modest response to this regimen has been seen in childhood malignant gliomas. This adjunctive regimen is also well tolerated by children (Geoerger et al., 2005).

Children with glioblastomas that exhibit methylation of the promoter for MGMT have a better prognosis than those without methylation of this promoter. They have a better response to temozolomide, presumably because they have silenced the production of MGMT, a DNA repair enzyme that could remove the alkyl groups that temozolomide put on O⁶ of guanine (Donson et al., 2007). Gefitinib, an EGFR tyrosine kinase inhibitor, is well tolerated in children and has similar pharmacokinetics in children as those in adults. It has been tried alone and with irinotecan in initial trials against malignant childhood brain tumors. Phase II data are not yet available. In vitro data suggest it causes radiosensitization of glioblastomas (Freeman et al., 2006).

Multidrug resistance of pediatric high-grade gliomas and glioblastomas is mediated by proteins, particular the ABC family of transporters, the regulation of which is complex and

altered by exposure to chemotherapeutic agents (Valera et al., 2008). Overcoming resistance to chemotherapy will be best served by an understanding of these regulatory mechanisms.

2.3. Low-grade glioma

Typically, low-grade gliomas of the brain in children are treated by surgery alone. In fact, some low-grade gliomas even regress spontaneously. The exception is tumors that are not surgically accessible without intolerable risk. For these, either radiation or chemotherapy has been used, but there are insufficient studies to define conclusively the roles of each (Abdullah et al., 2008; Rozen et al., 2008). In those instances where chemotherapy is used, the outstanding oncological prognosis of these tumors makes it all the more imperative that the drugs chosen engender tolerable toxicity. For this reason, vincristine and carboplatin are often the drugs of choice (Abdullah et al., 2008).

2.4. Brainstem glioma

The median survival of children diagnosed with brainstem gliomas is, at best, 9 months. Because of this, and in light of the sequelae of delivering high-dose radiotherapy to the developing central nervous system, attempts have been made to forestall radiotherapy by using chemotherapy primarily, with radiotherapy upon relapse or progression of tumor. One such recent attempt involved alternating cycles of hematotoxic and non-hematotoxic chemotherapeutic agents in patients with diffusely infiltrating pontine gliomas. BCNU and cisplatin were alternated with high-dose methotrexate. Median survival duration went from 9 months to 17 months but this regimen produced significant incremental toxicity, including infections, sometimes requiring hospitalization (Frappaz et al., 2008). Another smaller study examined the use of cisplatin, vincristine, fluvastatin, and thalidomide in patients with brainstem gliomas of mixed histologic types. These included glioblastomas, low-grade astrocytomas, and high-grade astrocytomas. Assessment was performed by MRI evaluation. Initial results showed a 71% survival at 24 months and a mean tumor volume that went from 20 to 9 cc. However, the small size of this series, the varied tumor types included (Lopez-Aguilar et al., 2008), and the difficulty in reproducibly assessing tumor size from MRI images (Hayward et al., 2008) make these results difficult to evaluate.

2.5. Ependymoma of the brain

Childhood ependymoma has been very difficult from a therapeutic standpoint. After surgical resection, 2/3 of children will have a recurrence. Cisplatin is the only single agent that has consistently shown efficacy. Craniospinal irradiation plus a posterior fossa boost results in cognitive decline. Reducing and focusing irradiation has reduced toxicity and enhanced efficacy (Grill et al., 2003). The resistant tumors overexpress P-gp. They also overexpress COX-2. Inhibition of COX-2 results in decreased expression and activity of P-gp and in induction of apoptosis in cultured ependymoma cells (Kim et al., 2004).

Current efforts include identification of molecular markers of invasive and migratory behavior that would earmark certain patients for adjuvant chemotherapy. Metalloproteinases appear to negatively influence prognosis and patients whose tumors express high levels of one or more of these proteins might well be selected for aggressive chemotherapy (Snuderl et al., 2008). Nucleolin expression and telomerase activation show promise as prognostic indicators (Ridley et al., 2008). Signaling molecules that are overexpressed in intracranial ependymomas include those that reflect the molecular signatures of the brain region of origin of the tumor, those that reflect the developmental stage of the tumor cells, and those that underlie the pathogenesis of the tumor and/or tumor recurrence (de Bont et al., 2008). Sorting this assignment out may lead to novel therapeutic approaches to this tumor.

2.6. Intracranial germ cell tumors

Intracranial germ cell tumors are generally divided into germinomas and non-germinomatous tumors. Germinomas are conventionally treated with radiation therapy; however, ongoing trials seek to reduce the required dose of radiation by using adjunctive chemotherapy. Germinomas are sensitive to many chemotherapeutic agents including cyclophosphamide, ifosfamide, cisplatin, etoposide, and carboplatin, with an 84% complete response rate. One Japanese study indicated that, although 92% of patients with low-grade pure germinomas treated with 3 cycles of chemotherapy followed by 24 Gy of focused radiation responded, 2.5 years later, 12% of these patients had recurrent disease (Echevarria et al., 2008).

Non-germinomatous tumors are considerably less radiation sensitive than germinomas. As such, adjunctive chemotherapy plays an important primary role in therapy. Platinum-based therapy affords 67–74% overall survival at a median of 53 months of follow-up (Echevarria et al., 2008).

2.7. Pituitary tumors

Craniopharyngeomas and pituitary adenomas are the most common intrasellar tumors of childhood (Jane, 2008). In adolescent patients with growth hormone-secreting tumors, the most common presenting symptom is amenorrhea (girls) and intracranial mass effect (boys); tall stature is common in both boys and girls. The best treatment paradigm involves primary somatostatin analogues followed by surgery and secondary somatostatin analogues (Colao et al., 2007). As is the case with craniopharyngeomas, primary surgery for pituitary adenomas often results in endocrinopathy, morbidity, and mortality; transsphenoidal therapy is therefore standard of care (Jane, 2008).

2.8. Tumors of the choroid

Tumors of the choroid are uncommon at any age. However, 80% of choroid plexus papillomas occur in childhood. They generally carry a poor prognosis because only 40 or 50% of these tumors can be completely resected surgically. The role of adjunctive chemotherapy is controversial at best, and has been proposed to be geared towards decreasing tumor vascularity before surgery (Gopal et al., 2008). Choroid meningiomas are even rarer; no role for chemotherapy has been proposed and treatment for these tumors is entirely surgical (Song et al., 2008).

2.9. Special considerations in brain tumors of infancy

Congenital brain tumors constitute 0.5–1.9% of all childhood brain tumors and the incidence is 0.34/million live births. Most are neuroectodermal tumors or medulloblastomas (Hon et al., 2006). Chemotherapy has a unique place in the therapy of infants because of the risks to the developing nervous system of radiation therapy. About a third of these children will respond well and not initially need radiation therapy, although most develop recurrent, progressive disease within 1 to 2 years. Chemotherapy therefore allows postponement of radiation therapy and decreases the toxicity of radiation therapy to the brain (Pollack et al., 2008).

There appear to be two subsets of infants with medulloblastoma. One includes patients with desmoplastic histologic features. These patients have an excellent prognosis, sometimes with only chemotherapy. The other includes patients with atypical teratoid/rhabdoid tumors. These patients have a particularly poor prognosis and the role of chemotherapy in their treatment is not yet clear (Gottardo and Gajjar, 2008).

Congenital glioblastoma has been reported and multimodal therapy often includes chemotherapy with temozolomide. The prognosis remains dismal (Hou et al., 2008).

3. Spinal cord tumors

Spinal cord tumors are 5–10% of CNS malignancies. Tumors of the spinal cord are most frequently cervical or thoracic. Astrocytomas are only infrequently resectable, while ependymomas are often resectable. Long-term survival is therefore more common with ependymomas, and mild neurological deficits are frequent (Nishio et al., 2000).

Spinal ependymomas most commonly occur as intramedullary tumors throughout the spinal axis. In the lumbosacral region, ependymomas are most commonly associated with the conus medullaris and cauda equina, but they can also occur extradurally in the sacrum, presacral tissues, or subcutaneous tissues over the sacrum. These two tumor locations produce different management concerns. Intradural ependymomas, especially those in the lumbosacral region, are now recognized for their potential to spread throughout the CNS, whereas extradural tumors elicit more concern for their association with extraneural metastases. Despite the risk for local recurrence and CNS dissemination, the prognosis for intradural lumbosacral ependymomas is good, with a greater than 90% 10-year patient survival in most series. The prognosis for extradural ependymomas does not appear to be as good. Much depends on extradural tumor location, however, and the outlook is better for dorsal sacral tumors than presacral tumors (Fassett and Schmidt, 2003).

Non-congenital sacral tumors in children are varied in pathological diagnosis. Radical resection appears to be effective in most cases (Lam and Nagib, 2002). A retrospective study performed at St. Jude on all comers with pediatric spinal cord tumors demonstrated that radical surgery is indicated for non-myxopapillary ependymomas and low-grade astrocytic tumors; the need for adjuvant chemotherapy should be determined by both tumor histologic type and extent of resection; and patients with disseminated juvenile pilocytic astrocytoma, ependymoma, and myxopapillary ependymoma may achieve long-term progression-free survival with craniospinal irradiation (Merchant et al., 2000).

4. Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood. It derives from cells of the peripheral neural crest and gives rise to tumors at loci along the sympathetic chain, most frequently in the chest or abdomen. For children with solitary primary tumors that are small enough that they do not cross the midline of the body, treatment consists of surgery alone and is effective to the point of cure in upwards of 95% of patients. However, for the 65% of patients whose tumors are either too large for complete surgical resection or metastatic to other tissues and organs at the time of initial diagnosis, current maximal available therapy, including surgery, chemotherapy, and radiation therapy, affords a 5-year survival rate of somewhere between 5 and 20%. Ablative chemotherapy followed by bone marrow transplantation to restore normal bone marrow cells wiped out by the chemotherapy converts this 5-year survival figure to an 8-year survival figure (reviewed in Schor, 2002). Clearly, a better understanding of the challenges of current conventional therapy and novel approaches to therapy for neuroblastoma are needed.

Clinical staging of neuroblastoma involves assessment of the magnitude of the tumor burden and the degree to which the tumor has disseminated. Stage I tumors are primary tumors that are small enough that they do not cross the midline of the body. Stage II tumors are also primary tumors, but, although they have not crossed the midline, they are too large to be removed surgically or have spread to lymph nodes near the tumor but not on the other side of the body. Stage III tumors have either themselves crossed the midline or have spread to lymph nodes nearby but on the other side of the body from the tumor. Stage IV tumors have spread to distant sites like lung, liver, and/or bone marrow and do not meet criteria for stage IV-S. Unique to neuroblastoma, stage IV-S or “special” tumors occur in children under the age of one year and

are generally small primary tumors that have spread to liver, bone marrow, and/or skin. Stage IV-S tumors are special because, despite their dissemination and unlike other disseminated neuroblastomas, they afford the patient an excellent prognosis (Evans et al., 1971; Evans et al., 1976).

4.1. Challenges of current conventional therapy

Drugs shown to have substantial efficacy against neuroblastoma include anthracyclines, platinum compounds, etoposide, vincristine, and alkylating agents. Neuroblastoma cells have a particular tendency to develop resistance; in general, the most aggressive therapy selects for the most difficult resistance. MRPs other than P-gp or MDR are thought to be responsible and to correlate with N-MYC gene copy number (Berthold and Hero, 2000). N-MYC-amplified neuroblastomas methylate the caspase 8 gene and do not express caspase 8. Caspase 8 acts as a tumor suppressor gene in these tumors (Teitz et al., 2001). The mainstay of neuroblastoma chemotherapy is combination therapy with cyclophosphamide, cisplatin, doxorubicin, and teniposide. Stage I patients and infants with stage 4S disease require and receive no chemotherapy; standard risk patients (N-MYC not amplified) and infants with symptomatic stage II-IV tumors receive chemotherapy to stop rapid tumor progression, treat life-threatening symptoms, or improve resectability of stage II or III disease. Carboplatin and etoposide or cyclophosphamide, doxorubicin, and vincristine are two alternative regimens. High risk patients receive ablative chemotherapy, which assumedly wipes out tumor but inevitably wipes out normal bone marrow, as well, plus bone marrow transplantation and granulocytic cell stimulating factor. Some centers “purge” the patient’s own bone marrow of neuroblastoma cells before reinfusing it into the patient, but it is not clear that bone marrow purging improves outcome (Berthold and Hero, 2000). The combination of ifosfamide, carboplatin, and etoposide elicited a major response in 15/16 children over age 1 year with stage IV neuroblastoma. Six of these 15 were disease-free at a median of 51 months (Donfrancesco et al., 2004).

4.1.1. Resistance to alkylating agents—Acquired resistance to alkylating agents is problematic for therapy. Loss of p53 may be a contributing factor. Tumor cells modulate their glutathione content in a p53-dependent manner (Goto et al., 2003). BSO, an inhibitor of GSH synthesis, synergistically enhances the cytotoxicity of the alkylating agent melphalan (Anderson et al., 2001), implying that GSH content may determine susceptibility to alkylating agents. BSO even enhances melphalan susceptibility of cells derived from patients who failed myeloablation followed by bone marrow transplant, but this still requires doses of melphalan that are as high as those used in the original myeloablation (Anderson and Reynolds, 2002).

4.1.2. Resistance to microtubule-inactivating agents—Vincristine is a highly effective microtubule-inactivating agent in the therapy of neuroblastoma. Vincristine-resistant neuroblastoma cells have been shown not to have mutations of α - or β -tubulin. Instead, MAP2c, a microtubule-associated protein, is markedly decreased; the microtubule destabilizing protein, stathmin, is greatly increased. Resistant cells have increased levels of polymerized tubulin and altered α - and β -tubulin content. Cellular morphology is greatly altered, as well (Don et al., 2004).

4.1.3. Resistance to DNA-cleaving agents—Doxorubicin and VP16 induction of apoptosis requires p53, MEK, H-Ras, and NF- κ B activation. Resistance relates to aberrations in this pathway (Armstrong et al., 2006). When SK-N-SH human neuroblastoma cells are doxorubicin resistant, conditioned medium from these cells decreases sensitivity to doxorubicin of sensitive SK-N-SH cells and induces them to activate the Akt survival pathway and inhibits activation of caspase 3, implying that humoral factors are secreted by the resistant cells that protect naïve cells from chemotherapy (Emran et al., 2002).

Schwann cell-like neuroblastoma cells treated with doxorubicin undergo apoptosis independent of death receptors and sensitive to inhibition of caspases 3, 7, and 9 but not to butylated hydroxyanisole (BHA) treatment. In contrast, neuron-like neuroblastoma cells treated with doxorubicin undergo necrosis not sensitive to inhibition of caspases and sensitive to BHA treatment, implicating reactive oxygen species in the mechanism of death (Hopkins-Donaldson et al., 2002). This implies that the two neuroblastoma cell subtypes may be differentially sensitive to doxorubicin in a given environment.

Cisplatin-resistant neuroblastoma cells overexpress DNA-methyltransferases. Inhibiting DNA-methyltransferases reverses this resistance (Qiu et al., 2002; Qiu et al., 2005). In one study, proteomic techniques were used to determine molecular accompaniments of neuroblastoma resistance to etoposide. The etoposide resistant clone showed overexpression of the following proteins: peroxiredoxin 1, β -galactoside soluble lectin binding protein, vimentin, heat shock protein, and heterogeneous nuclear ribonucleoprotein K. In addition, this study also revealed down-regulation of dUTP pyrophosphatase (Urbani et al., 2005).

4.1.4. Multidrug resistance—N-MYC overexpression in neuroblastoma cells leads to MDR1 overexpression and active P-gp, contributing to the chemoresistance of neuroblastomas (Blanc et al., 2003). However, several investigators have found that neither N-MYC overexpression nor chemoresistance correlates with MRP1 expression in these cells (Blanc et al., 2003; Goto et al., 2000). In contrast, others have found that MRP1 expression levels are higher in tumors that overexpress N-MYC than in those that do not and that high levels of MRP1 expression correlate with poor event-free survival rates (Haber et al., 2006). Still others present patient cohorts that demonstrate that expression levels of MDR1, MRP1, MRP5, or LRP are not predictive in neuroblastoma of response to therapy or occurrence of relapse (de Cremoux et al., 2007). While some groups find that MDR1 expression has no prognostic significance (Haber et al., 2006) and no correlation exists between P-gp or GST- π expression and outcome or patient characteristics (Kutlik et al., 2002), others indicate that MRP1 expression at the time of initial diagnosis conveys poorer prognosis (Goto et al., 2000). P-gp can be transferred from one neuroblastoma cell to another and allow the cells to resist high concentrations of drugs long enough to acquire endogenous P-gp (Levchenko et al., 2005). MRP-1 has been associated with poor prognosis in neuroblastoma in the past. MRP-4 also turns out to mediate chemoresistance in neuroblastoma. MRP-4 expression correlates with N-MYC expression (Norris et al., 2005).

Other mechanisms are also responsible for altering sensitivity of neuroblastoma to multiple drugs with different mechanisms. For example, hypoxia reduces sensitivity of neuroblastoma cell lines to vincristine, etoposide, and phenolic chemotherapeutic agents like VP16 but not to cytoxan. This reduction in sensitivity is related to up-regulation of HIF-1 α (Hyun et al., 2004; Hussein et al., 2006). Resistance to cisplatin cultivated in neuroblastoma cells in culture results in cross-resistance to N-methyl-N'-nitro-N-nitrosoguanidine, doxorubicin and vincristine, but not to Ara-C and chlorambucil. No changes in expression of MDR1, MRP, hMLH1 and hMSH2 were noted in these cisplatin-resistant cells (Iwasaki et al., 2002). In a murine xenograft model, antisense oligonucleotides to MRP1 enhanced apoptosis induction in neuroblastomas treated with VP16 (Kuss et al., 2002).

Many neuroblastomas that are drug resistant have lost either p53 or (more frequently) downstream p53 function. These resistant lines, more often than wildtype lines, express mutant p53 or overexpress MDM2. Furthermore, transduction with an HPV that degrades p53 renders sensitive cell lines resistant. This suggests that p53-independent mechanisms will be necessary to combat resistant neuroblastomas (Keshelava et al., 2001).

Knockdown of wildtype p53 in neuroblastomas confers MDR phenotype. Knockdown of mutant p53 does not. Senescence after DNA damage in neuroblastomas is p53-dependent; p53 knockdown results in mitotic catastrophe and subsequent apoptosis (Xue et al., 2007).

As is also the case for brain tumor cells, dexamethasone exposure can induce chemoresistance in neuroblastoma cells (Zhang et al., 2006).

4.2. Novel approaches to therapy

Novel approaches to therapy for neuroblastoma include: modulators of resistance-associated proteins; metabolic potentiators of conventional drugs; topoisomerase inhibitors; differentiating agents; apoptosis potentiators; modulators of signal transduction; targeted antineoplastic agents; anti-migration and/or -adhesion agents; anti-angiogenic agents; and immunotherapy (Berthold and Hero, 2000; Izbicka and Izbicki, 2005). Many new or developing strategies belong to more than one of these classes.

4.2.1. Modulators of resistance—Poland et al. (2005) describe an easy and practicable standardized technique that can be used to study global protein expression in chemosensitive and chemoresistant cancer cells to find candidate proteins that are potentially associated with the drug-resistant phenotype. Fractionation of human neuroblastoma cells using two-dimensional polyacrylamide electrophoresis, spot detection, image analysis, and finally protein identification is proposed as a means of individualizing strategies for overcoming resistance.

Chemoresponsiveness of neuroblastoma cell lines and the tumors developed from them in mice can be predicted from magnetic resonance spectroscopy before and after treatment. The methylene/choline ratio is predictive of responsiveness (Lindskog et al., 2004). Inhibition of MRP-1, a multidrug resistance protein linked to GSH conjugation of drugs, using VX710 along with paclitaxil showed some early promise in neuroblastoma. Alternatively, one can inhibit GSH synthesis with BSO to overcome resistance due to MRP1. Unfortunately, chemotoxicity increases as well. Overcoming MRP1-related resistance requires reducing GSH levels by 60–80% and non-toxic doses of BSO only reduce GSH by 30–40% (Bart et al., 2000). In neuroblastoma cell lines, expression of the longevity gene, *sirt 1*, results in expression of P-gp and resistance to chemotherapy, making *sirt 1* a possible chemotherapeutic target (Chu et al., 2005).

Ceramide is necessary for apoptosis enactment; conversion to glucosylceramide prevents this and mediates chemoresistance. Inhibitors of the conversion have been proposed as adjunctive chemotherapeutic agents. One such inhibitor did thwart chemoresistance, but the mechanism was not as predicted; it induced hyperploidy by a mechanism that does not involve enhanced ceramide accumulation (Dijkhuis et al., 2006).

Contributors to chemotherapeutic resistance in neuroblastomas include: down-regulation of caspase 8 by gene methylation (Fulda et al., 2001); conversely, enhanced transcription (via STAT-1) of caspase genes is reported in response to treatment with IFN- γ (Fulda and Debatin, 2002).

Prodrugs of etoposide have been designed that inhibit MDR-1 and are less toxic systemically. The maximum tolerated dose of these agents is three-times that of etoposide; the toxicity of these agents to neuroblastoma cells in vitro is >2-log higher than that of etoposide (Lange et al., 2003).

Onconase, a pancreatic RNase obtained from frog oocytes, is active against both native and multidrug resistant neuroblastomas both in vitro and in murine subcutaneous xenografted

tumors. It causes G1 arrest and caspase-independent cell death. It has a similar concentration- and dose-response curve in native and multidrug resistant cells (Michaelis et al., 2007).

Chemoresistant neuroblastoma cells secrete a protein into the medium that induces resistance in surrounding, otherwise sensitive cells. Transfection of the gene for this protein, midkine, into sensitive cells makes them resistant (Mirkin et al., 2005). This gene and protein are potential chemotherapeutic targets.

BBR3464 is a cisplatin analogue with multiple platinum-based nuclei and a putatively different DNA binding mechanism from cisplatin. It is effective in model systems vs. neuroblastoma cells that are cisplatin-resistant (Servidei et al., 2001). Gallium (III) organometallic complexes show promise in vitro in cisplatin-resistant neuroblastoma cells. Especially potent complexes contain halogen substituents on the phenolic rings; nitro substituents make the complexes less effective, but they still demonstrate apoptosis-inducing activity (Shakya et al., 2006).

In recent years it has become apparent that sphingolipid metabolism and the generation of sphingolipid species, such as ceramide, also play a role in drug resistance of neuroblastomas. This may involve an autonomous mechanism, related to direct effects of sphingolipids on the apoptotic response, and mechanisms dependent on a subtle interplay between sphingolipids and ATP-binding cassette transporters (Sietsma et al., 2002).

Induction of cathepsin L expression or inhibition of its degradation results in a senescent phenotype and reversal of neuroblastoma cell chemoresistance (Zheng et al., 2004).

4.2.2. Metabolic potentiators of conventional drugs—Ara-C is activated by phosphorylation by deoxycytidine kinase. Deoxycytidine kinase is feedback inhibited by high concentrations of dCTP. Therefore, drugs that deplete dCTP would be expected to enhance the activity of Ara-C. Cyclopentenyl cytosine (CPEC) is one such drug. Used adjunctively, CPEC enhanced the cytostatic activity of Ara-C against SK-N-BE(2)c human neuroblastoma cells. However, CPEC alone and in combination with Ara-C demonstrated similar levels of apoptosis induction (Bierau et al., 2003).

4.2.3. Topoisomerase inhibitors and DNA repair inactivators—Temozolomide plus cisplatin should be synergistic, as temozolomide prevents DNA repair of damage done by cisplatin. Only a modest response is seen in neuroblastomas. Temozolomide is, however, well tolerated by children (Geoerger et al., 2005).

A single case report indicates that irinotecan, a topoisomerase I inhibitor, cured stage III neuroblastoma in a 6 month old boy. The tumor was refractory to multiple other chemotherapeutic agents (Inagaki et al., 2005). In contrast, topotecan and CPT-11, two topoisomerase-I inhibitors, do not have significant activity against most etoposide- (i.e., topoisomerase-II-) resistant neuroblastoma cell lines and this suggests that agents other than topoisomerase inhibitors should be explored for the treatment of recurrent neuroblastomas (Keshelava et al., 2000). Oral topotecan has been proposed for therapy of refractory neuroblastoma. A trial of oral topotecan in 20 patients who failed multiple therapies including ablative therapy with bone marrow transplantation, was undertaken. Five patients achieved reduced tumor burden. Several patients had diarrhea necessitating dose reduction and, in one, cessation of therapy (Kramer et al., 2003).

4.2.4. Differentiating agents—Knockdown of XAB2, part of the corepressor complex that inhibits differentiation induction by retinoic acid, enhances the differentiating effect of all-trans retinoic acid on resistant neuroblastoma cells (Ohnuma-Ishikawa et al., 2007; see Fig. 2). N-MYC and c-myc overexpression conferred resistance to retinoic acid upon neuroblastoma

cells. However, these resistant lines were not resistant to the retinoic acid analog, fenretinide. In fact, some were more sensitive to fenretinide than were retinoic acid-sensitive lines (Reynolds et al., 2000). Fenretinide has since been shown to work by a reactive oxygen species-dependent mechanism distinct from that of differentiating agents (Lovat et al., 2004).

4.2.5. Apoptosis potentiators—Apoptosis incidence is not always reflective of chemotherapeutic potency against neuroblastoma (Russell and Ling, 2003). Neuroblastomas frequently lack caspase 8 and sometimes lack caspase 3. Caspase expression status does not correlate with N-MYC expression (Iolascon et al., 2003). Survivin protects neuroblastoma cells from apoptosis induction in a cell cycle-dependent manner. Cells in G2-M have abundant survivin and are resistant to apoptosis; cells in G1 have much less survivin and are sensitive to apoptosis. Retention of survivin in cells in G1 using ubiquitination inhibitors results in resistance to apoptosis induction (See Fig. 3). Perhaps survivin could be a target in enhancement of chemosensitivity of neuroblastoma (Chandele et al., 2004). Elevated survivin expression, altered expression of Bcl-2 family members, and amplification of MDM2, an inactivator of p53, are also reported in neuroblastoma (Fulda and Debatin, 2003).

Atypical retinoids (e.g., ST1926) kill neuroblastoma cells by a mechanism distinct from that of all-trans retinoic acid. It may be caspase-independent; it does not involve differentiation; it does not involve reactive oxygen species. ST1926 produces G2 arrest and cell-kill that is p53-independent (Di Francesco et al., 2007). Oxo-fenretinide is 4-times more potent than fenretinide against neuroblastoma and appears to work by a mechanism independent of retinoic acid receptors. Cells accumulate at the G2-M junction and undergo apoptosis by a mechanism that requires caspase-3 but not caspase-8 (Villani et al., 2006).

Tumor cell death from diallyl disulfide is dependent on reactive oxygen species generation; neuroblastomas are particularly susceptible. Adenocarcinomas have GSH reserves and peroxidase that protect them from such death. Decreasing GSH makes these tumors as susceptible as neuroblastomas. ERK 1/2 is involved in GSH-induced protection, as well (Filomeni et al., 2005).

Arsenic trioxide is effective against neuroblastoma cell lines even when the latter are resistant to conventional chemotherapeutic agents. This is true even under hypoxic conditions. Conventional chemotherapeutic agents, in contrast, are even less efficacious under hypoxia than under normoxia. Under both hypoxic and normoxic conditions, Bax gets cleaved after treatment of cells with arsenic trioxide, implying that the mechanism of cell death is the same under both sets of conditions (Karlsson et al., 2005). Arsenic trioxide has the capacity to kill multidrug-resistant neuroblastoma cells in vitro and in vivo and the drug is currently being evaluated in clinical trials (Pettersson et al., 2007).

Docosahexanoic acid is deficient in neuroblastoma cells relative to normal developing neurons. Supplementation of neuroblastoma cells with docosahexanoic acid (but not oleic acid) makes them more susceptible to chemotherapeutic agents and potentiates apoptosis induction. Depletion of GSH augments this effect; antioxidants like vitamin E dampen it (Lindskog et al., 2006).

Aphidicolin is selectively lethal to neuroblastoma cells and some other tumor cells but not to a host of normal cell types. It is not water soluble, and so, by itself, would not be usable for chemotherapy. However, it has been incorporated into a cyclodextrin inclusion complex and tested in murine subcutaneous xenograft models for effectiveness against native and vincristine-resistant neuroblastoma cell line tumors. It is equally effective against the native and resistant line tumors, and previous studies suggest that it is synergistic with other

conventional chemotherapeutic agents. It had no effect on the body weights or blood counts of the mice (Michaelis et al., 2001).

Engineered overexpression of N-MYC in SH-EP human neuroblastoma cells makes them more susceptible to apoptosis induction by chemotherapeutic agents of different mechanisms. They accumulate more DNA damage than N-MYC-negative cells. Microtubule inhibitors were the most potent of the chemotherapeutic agents in this system (Paffhausen et al., 2007).

Vitamin E analogues are toxic to neuroblastoma cells but not to differentiated neuroblastoma cells. Expression of Bcl-2 and Bcl-X_L and decreased expression of Bax decrease neuroblastoma sensitivity to these drugs, while siRNA to Bcl-2 and Bcl-X_L enhance sensitivity (Swettenham et al., 2005).

4.2.6 Modulators of signal transduction—In neuroblastoma cell lines, hypoxia-induced VEGF and flt-1 activation lead to bcl-2 overexpression and resistance to apoptosis through activation of ERK and MEK (Das et al., 2005).

GDNF has been said to have therapeutic potential for neuroblastoma. However, it sometimes increases chemoresistance and, along with neurturin, blocks the differentiating effects of retinoic acid (Hansford et al., 2005). BDNF and TrkB co-expression confers chemoresistance upon neuroblastomas. Transfecting TrkB into BDNF-expressing neuroblastomas renders them increasingly resistant. Trk inhibition reverses this. Also, TrkB-BDNF-expressing neuroblastomas constitutively phosphorylate Akt, whereas non-expressing neuroblastomas do not; this implies that the survival advantage of expressors is related to PI3K-Akt activation (Ho et al., 2002). TrkB activation by BDNF renders neuroblastoma cells resistant to chemotherapy of a whole host of mechanisms via activation of the PI3K pathway. Inhibitors of PI3K signaling may enhance sensitivity of these tumors to chemotherapy (Jaboin et al., 2002; Li et al., 2005).

Overexpression of Smac/DIABLO sensitized neuroblastoma to TRAIL. Activation of the TRAIL pathway has become an important method of inducing apoptosis except in TRAIL-resistant cells. However, treatment of these cells with other cytotoxic drugs sensitizes them to TRAIL, providing effective therapeutic advantages. In addition to activating apoptotic pathways, inhibition or suppression of cell proliferation is necessary to sensitize cancer cells to apoptosis. Critical among these proteins relevant to this effect are NF- κ B and Akt. Activated NF- κ B blocked apoptosis by interfering with the function of TNF α /TRAIL and/or through the activation of antiapoptotic proteins of the Bcl-2 family. Similarly, Akt mediates cell survival via the regulation of cell survival proteins and by blocking the function of proapoptotic Bad by phosphorylation. Altering the expression of Akt by dominant negative constructs or by expression of PTEN interferes with Akt function (Kumar et al., 2004).

Neuroblastomas are TRAIL resistant. This is said to be because they lack caspase-8. However, induction of caspase-8 expression does not restore TRAIL sensitivity to all neuroblastomas. This is because many lack TRAIL receptors. Adriamycin and etoposide induce TRAIL receptor expression. They can be followed by IFN- γ , which induces caspase-8 production and sensitivity to TRAIL (Yang et al., 2003).

Resistance of neuroblastoma cells in vitro to doxorubicin and MDL-28842 is accompanied by decreased signaling through the MAPK pathway, including decreased EGF responsiveness of MAPK pathway effectors (Mattingly et al., 2001; Mattingly, 2003).

Doxorubicin-resistant cells have up-regulated Stat3 signaling effectors and Bcl-X_L. Inhibiting Jak/Stat3 pathway signaling leads to enhanced sensitivity to doxorubicin. Doxorubicin-sensitive cells incubated with medium from doxorubicin-resistant cells become doxorubicin-

resistant and demonstrate activation of the Stat3 pathway (Rebbaa et al., 2001). This is another example of the activity of a presumed secreted factor inducing resistance in previously chemosensitive cells.

Inhibition of PKC β decreases chemoresistance of resistant neuroblastoma cell lines to doxorubicin, etoposide, paclitaxel, and vincristine but not carboplatin. It has no effect on sensitivity of non-resistant neuroblastoma lines (Svensson and Larsson, 2003).

Geldanamycin is a drug active against neuroblastoma that inhibits heat shock protein-induced protection from apoptosis. Differentiation of neuroblastoma cells with retinoic acid inhibits the activity of geldanamycin, assumedly because it inhibits nuclear translocation of p53 and activation of ERK and Akt. (Shen et al., 2007)

4.2.7. Targeted antineoplastic agents—An amphiphilic polymer based on a polyvinyl alcohol backbone [P10(4)] was synthesized as a potential “packaging” for chemotherapeutic agents, assuming it would be delivered to tumors like neuroblastoma because they are more likely to have aberrant, leaky blood vessels than normal tissues. In a murine metastatic disease model, P10(4), without chemotherapeutic drug loading, was effective as an anti-neuroblastoma and anti-melanoma agent, as determined by multiple parameters measuring apoptosis incidence, host survival, and tumor burden, and did not demonstrate systemic toxicity (Raffaghello et al., 2006).

Several experimental approaches to neuroblastoma exploit the neural characteristics of the tumor cells. Murine anti-human monoclonal antibodies have been aimed at the neuroblastoma-selective disialoganglioside, GD2. Antibody-bound neuroblastoma cells are earmarked for the host's reticuloendothelial system by virtue of the endogenous human anti-murine antibodies and killer T cells mobilized by the murine antibody-tagged cancer cells, and it is hypothesized that this approach will result in eradication of the GD2-bearing neuroblastoma cells with little or no toxicity to the host. Anti-GD2 murine IgG3 antibody 3F8 kills neuroblastoma cells by antibody-dependent cell-mediated cytotoxicity. Genetic factors influence clinical response to 3F8 and specific polymorphisms predict excellent outcomes (Cheung et al., 2006). More recently, ¹³¹I labeling of 3F8 has been used to target cytotoxic radioactivity to neuroblastoma cells (Dauer et al., 2007).

Based on the hypothesis that neurotrophins signaling through receptors on the surface of neuroblastoma cells exert protective effects on these cells, competitively inhibitory ligands have been examined as potential adjunctive agents for therapy of chemoresistant neuroblastomas (Fig. 4; Cortazzo et al., 1996; Yan et al., 2002a; Yan et al., 2002b). In addition, agonistic ligands of putatively pro-apoptotic neurotrophic receptors have been proposed for development as primary chemotherapeutic agents (Guillemard and Saragovi, 2004). The clinical utility of these agents is complicated by the variably pro- and anti-apoptotic function of the same receptor-ligand pair in different neuroblastoma cells within the same tumor. It is likely that effective targeting of signaling pathways must await identification of downstream, neuroblastoma-selective effectors.

The catecholamine uptake system on the surface of most neuroblastoma cells has been proposed for exploitation in neuroblastoma therapy. The oxygen radical-generating dopamine analogue, 6-hydroxydopamine, has been used *ex vivo* to “purge” neuroblastoma cells from patients' bone marrow prior to post-ablative chemotherapy bone marrow transplantation. Although the purging regimen does indeed get rid of neuroblastoma cells and the remaining marrow cells do engraft, the majority of patients develop recurrent disease in original tumor sites, implying that the so-called ablative chemotherapy does not completely rid the patient of tumor. Use of 6-hydroxydopamine *in vivo* is limited by toxicity to the normal sympathetic

nervous system, and several studies represent attempts to administer 6-hydroxydopamine adjunctively with agents that are selectively protective of normal cells (Schor, 1987; Schor, 1988; Purpura et al., 1996). TEMPOL, a stable nitroxyl radical superoxide dismutase mimic, shows promise in this regard (Purpura et al., 1996; Weinberg et al., 2004).

The antimitotic natural product, neocarzinostatin, is a prodrug that, when activated by sulfhydryl reduction, induces apoptosis in neuroblastoma cells. Schor (1992) used 6-mercaptodopamine, a dopamine analogue with a free sulfhydryl group, to selectively load neuroblastoma cells with reducing equivalents before treating cells with neocarzinostatin. Although this approach is effective in vitro, 6-mercaptodopamine forms a very hygroscopic gum and is unlikely to be pharmacologically tractable.

Finally, overexpression of antiapoptotic proteins of the Bcl-2 family, including Bcl-x_L, is a common mechanism of chemotherapeutic resistance in neuroblastoma cells (Dole et al., 1994; Dole et al., 1995). Bcl-2 overexpression in neural crest cells is associated with enhancement of GSH content and capacity for recycling GSH from its oxidized counterpart (Tyurina et al., 1997). This enhanced reducing potential led to the hypothesis that the activity of neocarzinostatin against neuroblastoma cells would be potentiated in those neuroblastomas that expressed particularly high levels of Bcl-2 or related proteins. Indeed, induction of apoptosis by neocarzinostatin is enhanced by the overexpression of Bcl-2 (Cortazzo and Schor, 1996). In fact, neocarzinostatin induces cleavage of Bcl-2 (26 kD) by caspase-3 to form a pro-apoptotic fragment (19 kD; Liang et al., 2002). This finding allows one to predict for which tumors neocarzinostatin would be likely to be efficacious. Tumors must express both caspase-3 and Bcl-2 in order for apoptosis induction to be enhanced (Mi et al., 2005; Rogers et al., 2008).

4.2.8. Anti-migration and/or -adhesion agents—Acquired neuroblastoma chemoresistance is accompanied by down-regulation of N-CAM which, in turn, leads to increased endothelial adhesion and increased invasiveness. Chemoresistance is correlated with increased malignant behavior. Transfection of N-CAM has also been shown in neuroblastoma and glioma cells to decrease invasiveness of tumor cells. Treatment of neuroblastoma cells with retinoic acid results in increased N-CAM expression, which may be responsible for the decreased level of malignancy of these cells after such treatment (Blaheta et al., 2006). Of interest, N-CAM expression is regulated by the p75 neurotrophin receptor (Mirnics et al., 2005); antagonists of NGF binding to this receptor may influence, not only tumor cell survival, but tumor cell adhesion, as well.

4.2.9. Anti-angiogenic agents—Resistant, sensitive, and revertant neuroblastoma cells were tested by genomic analysis. Resistant cells demonstrated down-regulation of pleiotrophin (heparin-binding growth factor) and less vasculature than sensitive neuroblastomas (Calvet et al., 2006). It has been contended that the vascular endothelium of tumors is of host origin and therefore genetically stable. However, N-MYC amplification can be found in the vessels of N-MYC amplified neuroblastomas, contesting this conventional notion (Pezzolo et al., 2007).

4.2.10. Immunotherapy—Cyclophosphamide with either iridotecan or topotecan/vincristine can be used effectively to prepare patients for immunotherapy for refractory neuroblastoma (Kushner et al., 2004). A novel, targeted IL-2 was formed by linkage of IL-2 to a monoclonal antibody to GD2. Toxicity was tolerable. No partial or complete responses were observed; but immunoreactivity to tumor was demonstrable in this Phase-I study (Osenga et al., 2006).

5. Conclusions

Tumors of the nervous system are among the most common and pharmacologically intractable neoplastic disorders of childhood and adolescence. Brain and spinal cord tumors exact a toll both directly and via the deleterious effects of radiotherapy upon the developing nervous system. Chemotherapy represents a means of avoiding or postponing radiotherapy in children with CNS malignancies. Malignant peripheral nervous system tumors include neuroblastoma, the most common extracranial solid tumor of childhood. Because of the frequency with which neuroblastoma is metastatic or otherwise surgically incurable at the time of diagnosis, treatment of this tumor often involves chemotherapy.

Novel approaches to tumors of the nervous system in childhood and adolescence are based on the expanding understanding of the molecular signatures of these tumors and their developing tissues and hosts of origin. Achievement of multimodal therapy that maximizes efficacy and minimizes toxicity depends critically upon integration and implementation of this knowledge base (Rogers et al., 2008; Mason and Cairncross, 2008).

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Abbreviations

BCNU	1,3-bis-(2-chloroethyl)-nitrosourea
BDNF	brain-derived growth factor
BHA	butylated hydroxyanisole
BSO	buthionine sulfoximine
CNS	central nervous system
CPEC	cyclopentenyl cytosine
DIABLO	direct inhibitor-of-apoptosis protein-binding protein with low pI
DNA	deoxyribonucleic acid
EGFR	epidermal growth factor receptor
ERK	extracellular signal-regulated kinase
GD2	disialylganglioside

GSH	reduced glutathione
GST	glutathione-S-transferase
HIF	hypoxia-inducible factor
IFN	interferon
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
N-CAM	neural cell adhesion molecule
P-gp	P-glycoprotein
PI3K	phosphatidyl-inositol-3-kinase
PKC	protein kinase C
PNET	primitive neuroectodermal tumor
PTEN	phosphatase and tensin homolog
Smac	second mitochondria-derived activator of caspase
TRAIL	TNF α -related apoptosis-inducing ligand
VEGF	vascular endothelial growth factor

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Fig. 1.

Distribution of primary CNS tumors of in a cohort ($n = 5,873$) of patients, age 0–19 years, in the U.S. (2000–2004). **(A)** Grouped by anatomic location of the tumor; **(B)** grouped by histological type of the tumor. Adapted from Central Brain Tumor Registry of the U.S. (2008).

Fig. 2.

Treatment of neuroblastoma cells with retinoic acid results in morphological differentiation and conversion of the cells to a mitotically quiescent state. The protein XAB2 is part of a complex that inhibits this activity of retinoic acid. Down-regulation of XAB2 expression with siRNA decreases this XAB2-mediated inhibition of retinoic acid and thereby restores its activity as a differentiation inducer. Red: anti-differentiation pathway; blue: pro-differentiation pathway.

Fig. 3.

Survivin is an anti-apoptotic protein expressed in some neuroblastoma cells. Its degradation is presaged by its ubiquitination. Inhibitors of this ubiquitination prolong the lifetime of survivin in the cell and thereby act in opposition to apoptosis-inducing chemotherapeutic agents. Red: anti-apoptosis pathway; blue: pro-apoptosis pathway.

Neuroblastoma Cells

Anti-apoptotic Signaling
Neurotrophin Receptor

Pro-apoptotic Signaling
Neurotrophin Receptor

Neurotrophin

Receptor-selective
Competitive Inhibitor

Fig. 4.

Neurotrophins can be pro- or anti-apoptotic depending upon the signaling events they trigger and the milieu in which they are expressed. Blocking anti-apoptotic signaling, but not pro-apoptotic signaling, with receptor-specific competitive antagonists of neurotrophic ligand binding has been proposed as a means of rendering neuroblastoma cells susceptible to chemotherapeutic attack.