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Neurotoxicity of Biologically Targeted Agents in Pediatric Cancer Trials

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Abstract

Biologically targeted agents offer the promise of delivering specific anticancer effects while limiting damage to healthy tissue, including the central and peripheral nervous systems. During the past 5-10 years, these agents were examined in preclinical and adult clinical trials, and are used with increasing frequency in children with cancer. This review evaluates current knowledge about neurotoxicity from biologically targeted anticancer agents, particularly those in pediatric clinical trials. For each drug, neurotoxicity data are reviewed in adult (particularly studies of brain tumors) and pediatric studies when available. Overall, these agents are well tolerated, with few serious neurotoxic effects. Data from younger patients are limited, and more neurotoxicity may occur in the pediatric population because these agents target pathways that control not only tumorigenesis but also neural maturation. Further investigation is needed into long-term neurologic effects, particularly in children.

Introduction

An increasingly robust body of literature has demonstrated adverse neurologic effects from cancer treatments, including surgery, traditional cytotoxic chemotherapy, and radiation. At the same time, significant advances in the understanding of the molecular pathways involved in tumorigenesis and proliferation have lead to the development of biologically targeted therapeutics. A recent focus of basic and translational cancer research has involved developing and testing therapeutic agents targeting extracellular, cell surface, and intracellular molecules that contribute to the development and progression of cancers and the resistance of tumors to conventional therapies [1]. Delivered individually or combined with chemotherapy or radiotherapy, molecularly targeted therapies have produced significant responses in certain types of cancer. In other malignancies, including brain tumors, cures have been elusive, but hope remains that current and future trials with rational combinations of therapies will be successful. The goal of targeted therapy with biologic agents involves selectively attacking the cancer cell and its supportive environment while sparing normal tissue, resulting in both increased efficacy and fewer short-term and long-

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term side effects, compared with traditional cytotoxic chemotherapy and radiotherapy. As these biologic agents are implemented in clinical trials, clinicians and clinician-researchers must be mindful of the potential for new or additional adverse effects, including neurotoxicity and adverse neurocognitive sequelae, particularly in children.

This review will describe what is known about neurologic side effects from biologically targeted agents that are undergoing pediatric clinical trials (summarized in Table 1). The names of the drugs alone and in combination with each of the search terms “neurotoxicity”, “toxicity”, “pediatric”, and “children,” as well as the knowledge of the authors, were used to generate a systematic review. Most published studies of these agents have been limited to phase I and some phase II studies of adults with refractory progressive and recurrent disease, although some pediatric studies have been described, and these are summarized in Table 2. Any deleterious effects on the developing nervous system may not be recognized until larger and longer-term studies of children have been performed. Nevertheless, this review may alert pediatric neurologists, oncologists, and other clinicians to potential side effects, and may aid in developing systematic approaches to studying and treating adverse neurologic sequelae.

Receptor Tyrosine Protein Kinase Inhibitors

Epidermal growth factor receptor inhibitors

Erlotinib (Tarceva; Genentech, South San Francisco, CA) was demonstrated to have minimal neurotoxicity. A randomized phase II trial in 2008 compared erlotinib with standard chemotherapy in 103 patients with advanced nonsmall-cell lung cancer, and reported that neuropathy occurred less frequently in patients treated with erlotinib (2% of patients) than in patients treated with carboplatin and paclitaxel (37% of patients) [2]. A phase I study of concurrent whole brain radiotherapy and erlotinib for multiple brain metastases from nonsmall-cell lung cancer revealed no treatment-related neurotoxicity in 11 patients [3]. Neurotoxicity was only reported when erlotinib is added to a regimen that already carries an increased risk of neurotoxicity. For example, adding erlotinib to a regimen of oxiliplatin, 5-fluorouracil, and leucovorin (FOLFOX) for metastatic colorectal cancer resulted in increased neurotoxicity that led to the removal of six patients from a trial of 35 patients (one because of ataxia, and five because of grade 3 peripheral neuropathy after therapy for 6-17 cycles) [4].

In pediatric phase I studies, erlotinib has been well tolerated. A phase 1 Children's Oncology Group study of 46 patients with multiple solid tumors, including central nervous system tumors, observed no neurotoxicity at a dose of up to 85 mg/m^2/day [5]. Another phase I study of 25 pediatric patients with high-grade glioma observed no neurotoxicity [6]. However, a multicenter phase I European study of 51 children with brainstem glioma and relapsing/refractory brain tumors observed intratumoral hemorrhages in three of 51 patients, and so this possibility must be considered [7].

Gefitinib (Iressa; AstraZeneca/Teva, Wilmington, DE) is another small molecule inhibitor of epidermal growth factor receptors. Multiple phase I and phase II clinical trials have not demonstrated significant neurotoxicity in adults with nonsmall cell lung cancer [8]. In a study of locally advanced head and neck cancers, grade 3 burning oral dysesthesia occurred in six of nine patients (67%) treated with gefitinib, paclitaxel, and radiation therapy. However, this adverse effect was associated with a high radiation dose to the tongue [9]. The main concern with gefitinib stems from case reports of brain hemorrhage in patients with brain metastases [10]. One phase III study of squamous cell carcinoma of the head and neck indicated a possible increase in intracranial hemorrhages [11]. Gefitinib has been tested in phase I and phase II trials of children with brainstem gliomas and supratentorial malignant

gliomas. A phase I study of 25 children with refractory solid tumors, including central nervous system malignancies, observed an intratumoral hemorrhage in one patient with an ependymoma treated at 500 mg/m^2/day [12]. In a phase I study of children with brainstem glioma, the dose-limiting toxicity involved the manifestation of intratumoral hemorrhages, which occurred in 5/20 patients at 250 mg/m^2/day or higher [13]. Furman et al. used gefinitib to enhance the bioavailability of irinotecan, and observed no adverse neurologic events in 29 pediatric patients with refractory solid tumors [14]. In a Pediatric Brain Tumor Consortium phase II trial of gefitinib and irradiation in children with newly diagnosed brainstem gliomas, three of 44 patients manifested an intratumoral hemorrhage, but no other adverse neurologic events [15]. Although the extent to which the natural history of the disease, treatment with gefitinib, additional treatments, or a combination of these factors is responsible remains unknown, intratumoral bleeding must be considered a possible adverse effect.

Lapatinib (Tykerb; GlaxoSmithKline, Research Triangle Park, NC) is a small molecule reversible inhibitor of epidermal growth factor. Multiple phase I and II studies of adult patients with solid tumors and metastatic carcinomas have not included neurotoxicity among common or serious adverse events [16]. One phase I study of lapatinib in combination with oxiliplatin/fluorouracil/leucovorin in patients with solid tumors found 14 cases of grade 1 neuropathy and four cases of grade II neuropathy. However, this result was thought more likely attributable to the oxaliplatin. A phase I study of lapatinib in 59 children with refractory or recurrent central nervous system malignancies observed no neurotoxicity other than fatigue [17].

Platelet-derived growth factor receptor inhibitors

Imatinib (Gleevac; Novartis, East Hanover, NJ) was primarily studied and used as a small molecule inhibitor of the bcr-abl tyrosine kinase that is characteristic of chronic myeloid leukemia, but also inhibits c-kit and platelet-derived growth factor receptor, which is present in many gliomas. It may also be antiangiogenic. In terms of neurologic side effects, it has been associated with muscle cramping, myalgias, and reports of intracranial bleeding in adults [18]. In pediatric studies, no significant neurotoxicity was reported in several phase I and phase II studies of imatinib in children with Ph + acute lymphoblastic leukemia and Philadelphia Chromosome + acute myelogenous leukemia [19-21]. A phase I study of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas reported high rates of intratumoral hemorrhage, although the authors cautioned that the incidence of spontaneous hemorrhage in brainstem glioma is not well characterized. Nevertheless, the dose recommendation for phase II studies was lowered to 265 mg/m^2 because of these hemorrhages [22]. In addition, multiple case reports and a retrospective study of children with chronic myeloid leukemia raise concerns about the impairment of prepubertal growth in children treated with long-term imatinib [23].

Vascular endothelial growth factor inhibitors

Bevacizumab (Avastin; Genentech/Roche) is a monoclonal antibody targeted against all forms of the vascular endothelial growth factor. The vascular endothelial growth factor and its downstream mediators, such as nitric oxide, play a key role in maintaining vascular integrity. Therefore, vascular endothelial growth factor inhibitors are also considered antiangiogenic. These agents have been used to treat age-related macular degeneration as well as various malignancies. The reported neurotoxicity for this class of drugs includes cerebrovascular accidents, hypertension, posterior reversible leukoencephalopathy syndrome, radiation necrosis, and bleeding.

Concerns have arisen about increased cardiovascular and cerebrovascular events associated with vascular endothelial growth factor inhibitors. A recent meta-analysis of prospective clinical trials, including 859 patients, revealed an association between intravitreal injections of the vascular endothelial growth factor monoclonal antibody ranibizumab and the subsequent incidence of cerebrovascular accidents [24]. However, another meta-analysis of 12,617 patients from 20 randomized clinical trials found that bevacizumab was associated with an increased incidence of arterial thromboembolic events, particularly in patients with renal cell carcinoma and colorectal cancer, but not an increased incidence of stroke [25]. Therefore, to what extent, if any, vascular endothelial growth factor inhibitors increase the incidence of stroke during or after treatment remains unclear.

Vascular endothelial growth factor inhibitors are known to cause hypertension, possibly putting patients at risk for increased cerebrovascular events. A trial of bevacizumab compared with placebo on top of standard therapy for colorectal cancer revealed that bevacizumab increased the incidence of new-onset hypertension (22.4% vs 8.3%) and grade 3 hypertension (11.0% vs 2.3%) [26]. Different vascular endothelial growth factor inhibitors carry different risks of hypertension, and the frequency for all grades of hypertension associated with vascular endothelial growth factor inhibition is reported to be 20-30% with bevacizumab and 15-60% with small molecule tyrosine kinase inhibitors [27]. Poorly controlled hypertension may lead to posterior reversible leukoencephalopathy syndrome in patients treated with vascular endothelial growth factor inhibitors, although this finding occurs in less than 1% of patients [28,29].

Radiation necrosis may also be worsened by vascular endothelial growth factor inhibitors. Kelly et al. recently reported on four cases of late radiation-induced neurotoxicity with bevacizumab after radiotherapy to the central nervous system, including three cases of optic neuropathy and one case of myelopathy [30]. The adverse neurologic effects occurred 6-24 months after completing radiotherapy, and as soon as 10 days after commencing bevacizumab. The authors hypothesized that bevacizumab may increase the risk of late radiation neurotoxicity by inhibiting the vascular endothelial growth factor-dependent repair of normal neural tissue. Paradoxically, in other studies, bevacizumab was proposed as a potential therapy to treat radionecrosis by inhibiting vascular endothelial growth factor-promoted blood-brain barrier dysfunction, and decreasing capillary leaking and brain edema [31,32]. Clearly, more research is needed to determine the effects of bevacizumab on radiation necrosis.

After a study in 2003 indicated an increased incidence of intratumoral bleeding and thrombotic events in patients with metastatic colorectal cancer treated with bevacizumab, concerns about coagulopathy and bleeding led to the exclusion of patients with central nervous system metastases in many clinical trials [33,34]. However, a review in 2008 of 10,500 patients in 57 trials, including four trials of patients with brain metastases, concluded that the rate of intracranial bleeding was negligible, and that patients with central nervous system metastases should be included in trials of bevacizumab [35]. Another meta-analysis in 2008 of nearly 8000 patients in 15 randomized clinical trials revealed an increased risk of both all-grade and clinically significant high-grade thromboembolism (incidence, 12%; relative risk, 1.3), but not bleeding, in patients treated with bevacizumab at both low and high doses, with a higher risk in renal cell cancer [36]. Furthermore, anticoagulation with lovenox or warfarin did not lead to an increased risk of bleeding in a study of 21 patients with gliomas treated with bevacizumab [37], nor in a review of three studies in which patients received both bevacizumab and anticoagulation [38]. Those authors concluded that anticoagulation is not a contraindication to initiating bevacizumab. Studies of bevacizumab for recurrent malignant gliomas reported that intracranial hemorrhages occurred in less than 4% of patients, and were severe in only approximately 1% of patients [28]. Poor wound

healing is of particular concern for patients undergoing neurosurgery and radiation therapy [39].

In terms of pediatric studies of bevacizumab, a single-institution review of eight children with recurrent or progressive high-grade gliomas treated with bevacizumab revealed no instances of hypertension, intratumoral hemorrhage, or cerebrovascular events [40]. Another review of 12 children revealed one instance of grade III delayed would healing [41]. A Pediatric Brain Tumor Consortium study of irinotecan and bevacizumab in 31 pediatric patients with high-grade gliomas revealed hypertension in seven patients, grade 4 central nervous system ischemia in two patients, and grade 1 central nervous system hemorrhage in four patients, which according to the authors fell within the baseline risk for brainstem gliomas in the absence of antiangiogenic therapy [42]. In a study of bevacizumab and irinotecan to treat multiply recurrent low-grade gliomas in 10 children, including three with neurofibromatosis type 1, one case of transient leukoencephalopathy was reported, with no significant neurotoxicity otherwise [43]. Because strokes are increased in both children undergoing treatment for brain tumors and survivors of brain tumors, longer follow-up studies are needed for children treated with vascular endothelial growth factor inhibitors. Pediatric clinical trials of other monoclonal antibodies inhibiting the vascular endothelial growth factor, including PTC 299 and cediranib, are underway, with no results published to date.

Downstream Signal Transduction Pathways

Ras/Raf/mitogen-activated protein kinase/extracellular signal-related kinase pathway

Farnesyltransferase inhibitors—Tipifarnib (Zarnestra; Johnson & Johnson, New Brunswick, NJ) is a farnesyl transferase inhibitor that blocks the main post-translational modification of proteins such as Ras. Tipifarnib has been tested in phase I and II studies in leukemias and phase I, II, and III studies in solid tumors. Overall, nonhematologic toxicity was limited in frequency and severity. Peripheral neuropathy occurred in a significant number of patients treated with tipifarnib for advanced breast cancer. However, an intermittent dosing schedule was associated with a significantly reduced incidence of neurotoxicity [44]. A phase II study of tipifarnib in 28 adults with myelodysplastic syndrome reported headache in 36%, dizziness in 21%, and mild “neurotoxicity” (type not specified) in 11%, with no grade 3 or 4 neurotoxicity reported [45]. An exposure vs response analysis of five adult clinical studies involving more than 600 patients reported grade 2 or higher central nervous system neurotoxicity in 25% and peripheral neurotoxicity in 10% of patients, and these findings were significantly associated with the area under the curve (exposure). The mean time to occurrence for the worst grade of central nervous system toxicity was 243 days, illustrating the possible slow onset of signs and the need for long-term follow-up [46]. With regard to studies of adults with brain tumors, one phase I study of 89 patients with recurrent malignant glioma revealed no neurotoxicity [47], and a phase II trial of 28 adult patients with newly diagnosed glioblastoma described one instance of motor neuropathy, one instance of sensory neuropathy, and one other (unspecified) neurologic adverse event [48]. Furthermore, the combination of tipifarnib and capecitabine in 41 adult patients with refractory solid tumors resulted in no dose-limiting or frequent neurotoxicity, except for five episodes of grade 3 fatigue [49].

In a pediatric phase I study of tipifarnib with 29 patients receiving 300 mg/m^2/dose, neurotoxicity was infrequent and mild [50]. In another phase I trial of 17 children receiving tipifarnib and radiotherapy for a newly diagnosed diffuse intrinsic pontine glioma, one patient developed punctuate microhemorrhages in the temporal and occipital lobes and right parietal region, increased T_1-weighted and T_2-weighted signals in subcortical regions, and Klüver-Bucy syndrome after eight cycles. This toxicity was characterized as a grade 3, and

the radiographic and clinical changes slowly improved after discontinuation of the drug [51]. Another phase I pediatric study of 21 patients with refractory solid tumors and 17 patients with neurofibromatosis type I-associated plexiform neurofibromas reported no neurologic dose-limiting toxicities [52]. Single reports of grade 1 or 2 neurologic toxicities included dizziness, somnolence, insomnia, sensory neuropathy, and increased thirst. A pediatric phase II study of tipifarnib for recurrent or refractory high-grade glioma, brainstem glioma, and medulloblastoma also reported that the drug was well tolerated [53]. Of 91 patients, two manifested grade 3 motor neuropathy, two manifested seizures, one manifested fatigue, one manifested confusion, one manifested mental status changes, one manifested syncope, one manifested visual impairment, and one manifested headaches. No grade 4 neurologic toxicities were reported.

Raf inhibitors—Sunitinib (Sutent; Pfizer, Inc., New York, NY) and Sorafenib (Nexavar; Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ, and Onyx Pharmaceuticals, Inc., Emeryville, CA) are orally bioavailable, small-molecule tyrosine kinase inhibitors with similar properties. They target platelet-derived growth factor in addition to vascular endothelial growth factor, Flt-3, Ret, Kit, Raf, and colony-stimulating factor. As with other antivascular endothelial growth factor agents, these agents have been associated with hypertension, thrombotic microangiopathy, and posterior reversible leukoencephalopathy syndrome [54-56]. Posterior reversible leukoencephalopathy syndrome, which may also occur during traditional chemotherapies including cyclophosphamide and methotrexate, manifests as seizures, cortical blindness, and altered mental status, and is associated with increased magnetic resonance imaging T_2 signals most typically of the parieto-occipital white matter, but may include anterior regions and cortical gray matter. Although the supportive management of hypertension and seizures usually results in recovery from posterior reversible leukoencephalopathy syndrome, and oncologists often resume treatment with the offending agent, no controlled studies have examined this practice, either with traditional chemotherapy or new biologic agents.

Rates of hypertension are reportedly lower than with other vascular endothelial growth factor inhibitors such as bevacizumab and cederinib, because they bind to other tyrosine kinases with greater affinity than to vascular endothelial growth factor [57]. However, a positive relationship between diastolic blood pressure changes and total sunitinib dose was reported by a large pharmacokinetic/pharmacodynamic meta-analysis [58]. A phase I study of 39 adult patients with advanced solid tumors indicated that the combination of sunitinib or sorafenib with bevacizumab causes earlier-onset, more frequent, and more severe hypertension than with these drugs as single agents [59]. As already described, hypertension can lead to neurologic adverse events, including posterior reversible leukoencephalopathy syndrome (with associated seizures, vision impairment, and encephalopathy) and stroke, although these events are rare. A recent retrospective analysis, pooling safety and efficacy data from four adult studies, observed that cerebrovascular events were rare in patients treated with sunitinib, and the authors suggested that sunitinib-associated hypertension may provide an efficacy biomarker, because it is associated with improved clinical outcomes without clinically significant increases in hypertension-associated adverse events [60]. Caution should be exercised in extrapolating findings from adult studies reporting hypertension in patients with tumors that affect the vasculature (including renal cell carnimoma and hepatocellular carcinoma), or from patients who already manifest underlying hypertension, to pediatric patients, in whom underlying hypertension is much less common.

Although concerns exist about cerebrovascular complications with any drug that targets tumor vasculature and tumor-associated neo-angiogenesis, small-molecule tyrosine kinase inhibitors seem to be associated with fewer intracranial hemorrhages than vascular endothelial growth factor monoclonal antibodies. A phase I study of sunitinib in previously

treated, advanced nonsmall-cell lung cancer reported one death from cerebral hemorrhage in a 73-year-old patient with brain metastases [61]. Other neurotoxicities included grade 3 or 4 fatigue/asthenia (29%) and pain/myalgia (17%). Another study examined 106 patients with spinal or cerebral metastatic lesions from renal cell carcinoma who were treated with sorafenib or sunitinib with simultaneous single-fraction radiosurgery; although two patients manifested tumor hemorrhage, these hemorrhages were asymptomatic [62]. In the first published pediatric trial of sunitinib in 31 patients with refractory solid tumors, fatigue was the only neurotoxicity reported, and was not dose-limiting [63].

Mitogen-activated protein kinase inhibitors—Selumetinib is a potent, selective inhibitor of the mitogen-activated protein kinase in the Ras/Raf/mitogen-activated protein kinase/extracellular signal-related kinase pathway, with efficacy in several tumor models. It has been used in multiple phase II studies of adult malignancies, including pancreatic cancer, hepatocellular carcinoma, biliary cancers, and leukemia. Fatigue is common, but no other significant neurotoxicity has been reported [64]. No studies of mitogen-activated protein kinase inhibitors in pediatric malignancies have yet been published, although such drugs are under active study.

Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin pathway

Mammalian target of rapamycin inhibitors—Sirolimus (Rapamycin; Pfizer, Inc.) has been tested in phase II studies of adults with refractory and advanced renal cell carcinoma, advanced breast cancer, mantle cell lymphoma, and glioblastoma, and has proven to be safe at a range of doses [65]. Sirolimus is commonly used to manage organ rejection in children, and posterior reversible leukoencephalopathy syndrome is a known but rare side effect [66]. A retrospective report of 313 pediatric and adult cardiac transplant patients treated with immunosuppressive agents at the Mayo Clinic (Rochester, MN) revealed no major neurotoxicity in 116 patients treated with sirolimus, whereas seizures, posterior reversible leukoencephalopathy syndrome, and cerebrovascular events were evident in patients treated with cyclosporine [67]. A recent pediatric clinical series demonstrated clinical responses to single-agent sirolimus in subependymal giant cell astrocytomas and a low-grade glioma in five patients aged 3-21 years with tuberous sclerosis, with no adverse neurologic effects [68].

The sirolimus ester temsirolimus (CCI-779; Pfizer, Inc.) has been studied in phase I and II trials of multiple tumor types, including brain tumors in children and adults. A phase I study of temsirolimus in adult patients with treatment-refractory solid tumors revealed that a weekly infusion of temsirolimus at doses of 7.5-220 mg/m^2 resulted in no dose-limiting neurotoxicity and no frequent neurotoxicity [69]. In a phase II study of 85 patients undergoing induction chemotherapy for extensive-stage small cell lung cancer, weekly “consolidation” treatment with temsirolimus at 25 or 250 mg daily caused no grade 3 or 4 neurotoxicity [70]. Treatment with temsirolimus in 110 patients with renal cell carcinoma also resulted in no significant neurologic toxicity [71]. In 35 older adult patients with mantle cell lymphoma receiving 250 mg of temsirolimus weekly, one case each was reported of grade 3 muscle weakness, motor neuropathy, cranial neuropathy, blurred vision (in a patient with cytomegalovirus retinitis) and headache, and grade 4 decreased consciousness [72]. In a phase II randomized study of 109 patients with relapsed, progressive, advanced-stage breast cancer treated with 75 mg or 250 mg temsirolimus weekly by vein, depression and somnolence were the only grade 3 or 4 neurologic toxicities, occurring in 5% and 6% of patients, respectively. Depression and somnolence of any grade occurred in 16% and 28% of patients, respectively, and both were slightly less common in the low-dose group [73].

In terms of brain tumor studies, a North Central Cancer Treatment Group phase II trial of temsirolimus administered to 65 adult patients with recurrent glioblastoma multiforme indicated that neurotoxicity was rare, with fewer than 5% of patients experiencing grade 3 or 4 confusion, anxiety, neurosensory signs, neuromotor signs, or headaches that could be classified as at least possibly related to treatment [74]. Another phase II study in adults with glioblastoma reported no major neurologic events for 6 months when administering temsirolimus weekly at a dose of 250 mg intravenously to patients on enzyme-inducing antiepileptic drugs, or 170 mg for patients not receiving enzyme-inducing antiepileptic drugs [75].

Everolimus has been tested in phase I and II studies of advanced solid tumors and metastatic renal cell carcinoma, and is also being used in pediatric trials. A phase I study of everolimus and paclitaxel in 16 adult patients revealed no neurologic dose-limiting toxicity and only two cases of possible treatment-related headache [76]. A recent open-label study demonstrated significant responses to everolimus in 28 pediatric patients with tuberous sclerosis and subependymal giant cell astrocytomas, treated for a mean of 21.5 months, and reported no significant adverse neurologic effects [77]. In that study, a reduction of clinical and subclinical seizures, improvements in self-reported quality of life scores, and no changes in neurocognitive performance were reported.

Protein kinase B inhibitors—Perifosine (KRX-0401; Keryx Biopharmaceuticals, Inc., New York, NY) was the first-in-class oral anticancer agent that inhibits the activation of protein kinase B in the phosphoinositide 3-kinase pathway. Perifosine was tested in multiple phase I studies of noncentral nervous system tumors, and the predominant dose-limiting toxicities included gastrointestinal toxicity and fatigue. Phase II studies of advanced metastatic breast cancer, adenocarcinoma, and soft tissue sarcoma revealed no adverse neurologic affects attributable to the medication [38]. Although perifosine has demonstrated some promise in preclinical studies of brain tumors, this finding has yet to be translated to clinical trials, and therefore the possible neurotoxicity in brain tumor patients remains unknown. No clinical trials of protein kinase B inhibitors in brain tumors or in pediatric malignancies have been published. The agent MK 2206 is currently being tested in a phase I study of recurrent and refractory malignant solid tumors and leukemia.

Other antiangiogenetic agents—Thalidomide can be classified as an antiangiogenetic or immunomodulatory drug. Aside from its teratogenicity, the major neurotoxicity of thalidomide involves peripheral neuropathy. A phase II study of patients with multiple myeloma reported mild to moderate distal sensory neuropathy in 20-40% of patients and motor neuropathy in less than 10% of patients, and the presence and severity of peripheral neuropathy were associated with the duration of medication [78]. The neuropathy may progress even after the drug is discontinued, and permanent neurologic disability may result if the drug is not discontinued when neuropathy is first detected on examination. Therefore, neurologists should monitor for neuropathy closely, and recommend drug discontinuation early in the course of neurotoxicity.

Recently, thalidomide was used to treat a number of pediatric conditions, including optic neuritis, juvenile Behçet disease, early-onset sarcoidosis, and intractable inflammatory bowel disease, with 25% of these patients reportedly experiencing reversible neuropathy [79]. In an open-label study of thalidomide to treat juvenile rheumatoid arthritis, transient paresthesias were common and required dose reduction in 4/13 patients. However, the authors did not specify the indications for dose reduction, and stated that no clinically apparent neurotoxicity was observed [80]. A phase II study of thalidomide and cyclophosphamide in 27 pediatric patients with refractory malignancies reported no

significant neurotoxicity. However, the study failed to show efficacy, and patients may not have received the medication long enough to develop such side effects [81].

Lenalidomide (Revlimid; Celgene, Summit, NJ) is a potent structural and functional analogue of thalidomide that similarly demonstrates immunomodulatory, antiangiogenic, proapoptotic, and anti-inflammatory effects. Reports to date indicate that lena-lidomide does not cause the neurotoxicity observed with thalidomide, and a placebo-controlled trial of 356 patients indicated that grade 3 or 4 somnolence, constipation, or peripheral neuropathy (all toxic effects of thalidomide) occurred in less than 10% in patients treated with lenalidomide, rarely resulting in a dose reduction [82]. A consensus panel statement supports the long-term use of lenalidomide in multiple myeloma, in consideration of how well tolerated the medication has proved [83].

Two trials of lenalidomide in children have been reported. The Pediatric Brain Tumor Consortium performed a phase I trial of lenalidomide in 51 pediatric patients with recurrent, refractory, or progressive primary central nervous system tumors. The drug was revealed to be tolerable in children with central nervous system tumors at doses of 116 mg/m^2/day, with no neuropathy [84]. One case of grade 3 dizziness and one case of grade 4 fatigue were reported, but the fatigue occurred in a patient with disease progression, and was not necessarily attributable to the medication. A Children's Oncology Group study in 2011 of lenalidomide in 49 patients aged 1-21 years with recurrent or refractory solid tumors or myelodysplastic syndrome reported no dose-limiting toxicity at a maximum tested dose of 70 mg/m^2/dose [85].

Sonic Hedgehog pathway inhibitors—The first clinical trial of the hedgehog pathway inhibitor GDC-0449 (Vismodegib; Roche, Basel, Switzerland) in solid tumors included 33 patients with locally advanced or metastatic basal cell carcinoma, and revealed no neurotoxicity other than a few possible instances of grade 3 muscle spasm and fatigue [86]. Another study of 66 adult patients, most with basal cell carcinoma and one with medulloblastoma, reported one case of grade 4 presyncope and no significant neurotoxicity otherwise [87]. One case report of GDC-0449 in a 26-year-old patient with medulloblastoma described no neurotoxicity from the drug [88], and clinical trials of this drug are underway. Thus, GDC-0449 appears to be safe from the standpoint of neurotoxicity in adults, but no pediatric studies have been published. Because the Hedgehog signaling pathway is a key regulator of cell growth and differentiation during development, short-term and long-term studies of children are needed.

Notch signaling: γ-secretase inhibitors—Gamma-secretase inhibitors inactivate Notch signaling and suppress angiogenesis. They represent another promising molecularly targeted antineoplastic therapy, especially for patients manifesting tumors with constitutive Notch activation [89]. Phase I trials of multiple agents are underway in adults and children. Published clinical trials for this class of drugs are limited to patients with Alzheimer disease. In early studies, the major side effect constituted peripheral cytotoxicity, particularly of the gastrointestinal tract. A phase II study of LY450139 (Semegacestat; Eli Lily, Indianapolis, IN) indicated increased somnolence, fatigue, lethargy, and asthenia in patients receiving the medication [90]. Recently, a phase III trial of this agent was discontinued because preliminary results demonstrated no effect or a mild worsening of cognition. This failure was attributed to variable effects from signaling pathways triggered by γ-secretase substrates, as well as poor specificity for the amyloid precursor protein, which the drug was meant to decrease [91]. Preclinical studies of γ-secretase inhibitors indicated subtle learning deficits in Notch-1 heterozygous knockout mice, and progressive neurodegeneration in mice with both copies of the γ-secretase component *PS-1* gene knocked out [92]. Therefore, some concern has arisen that the loss of γ-secretase activity and decreased Notch function in the

brain may impair cognition in patients treated with these agents, and further investigation is needed.

Histone deactylase inhibitors—Suberoylanilide hydroxamic acid (Vorinostat; Patheon, Research Triangle Park, NC) is a histone deacetylase inhibitor whose anticancer effects are based on the fact that malignant cells resemble immature progenitor cells capable of terminal differentiation, which may abort aberrant growth. Suberoylanilide hydroxamic acid has been well tolerated, and its most common side effects include nausea, diarrhea, and fatigue. In a study of 37 adult patients with acute myeloid leukemia, one case of grade 4 central nervous system hemorrhage and one case of grade 4 dizziness occurred [93]. Other than fatigue, which can be serious, adverse neurologic events have not been observed in phase I studies of Vorinostat in prostate cancer, diffuse large B-cell lymphoma, and multiple myeloma. In 66 adult patients with glioblastoma multiforme, no adverse neurologic events were evident except for fatigue, which occurred in more than 50% of patients and was mostly grade 1 or 2 [94]. When used in combination with carboplatin and paclitaxel for advanced solid malignancies (including four tumors of the head and neck), nondose-limiting neuropathy was reported, but with no indication that Vorinostat increased the likelihood or severity of carboplatin-induced neuropathy [95]. No pediatric studies have been performed. When developmental toxicity was assessed in rats and rabbits, Vorinostat did not induce morphologic malformations, although at high doses it was associated with decreased fetal weight and skeletal variations [96]. The authors concluded that the teratogenicity of Vorinostat and valproic acid (Depakote) is not attributable to histone deacetylase inhibition. A phase I Children's Oncology Group trial indicated that suberoylanilide hydroxamic acid is well tolerated in patients with recurrent solid tumors at 230 mg/m^2/day, with no serious neurotoxicity [97].

Valproic acid (Depakote; Abbott, Abbott Park, IL), an antiepileptic medication that has been used extensively in children with epilepsy and mood disorders for over 30 years, inhibits class I and class IIa histone deacetylase, and was recently used for its anticancer properties. Valproic acid was relatively well tolerated in phase I and phase II studies of adults with solid and hematologic malignancies; somnolence and confusion were the most common central nervous system toxicities. A study from the M.D. Anderson Cancer Center (Houston, TX) of 44 heavily pretreated pediatric patients with high-grade glioma or diffuse, intrinsic pontine glioma reported treatment-related somnolence in three patients, but no dose-limiting neurotoxicity [98]. A phase I Children's Oncology Group study of 26 patients with refractory or recurrent solid tumors, including central nervous system tumors, described dose-limiting somnolence in several patients at troughs of 100-150 mg/mL, and grade 1 and 2 dizziness, fatigue, somnolence, and headache at troughs of 75-100 mg/mL [99]. Mild thrombocytopenia was common, and one intratumoral hemorrhage occurred in a patient with a lung mass, but no instances of central nervous system hemorrhage were observed. The authors also reported that in an ongoing phase II trial of valproic acid and radiation, followed by maintenance valproic acid and bevacizumab in children with newly diagnosed high-grade or brainstem gliomas, no neurotoxicity was evident in the seven children treated to date.

Proteasome inhibitors—Bortezomib is a proteasome inhibitor whose use has been limited by its peripheral neurotoxicity. In one series, nine of 78 treated patients had to discontinue the drug because of peripheral axonal neuropathy. Studies indicate a distal loss of all sensory modalities in the lower limbs in about 35% of cases, predominating in the small fibers with neuropathic pain, and less than 10% of patients manifested associated mild distal weakness. However, these findings must be interpreted with caution, because many patients in the study exhibited a preexisting neuropathy from myeloma or previous chemotherapy [100].

A few phase I pediatric clinical studies examining bortezomib as add-on therapy to multiple chemotherapies in children with refractory disease reported the drug to be well-tolerated. One phase I study of bortexomib in 15 children with refractory solid tumors demonstrated no neurotoxicity, and another phase I study of 12 pediatric patients with refractory leukemia described one case of grade 3 confusion, and no neurotoxicity otherwise [101,102]. Results should be interpreted with caution, however, because treatment courses were brief. A study of bortezomib added to four-drug induction chemotherapy with vincristine, dexamethasone, pegylated L-asparaginase, and doxorubicin in 10 children with relapsed, acute lymphoblastic leukemia demonstrated that toxicity was predictable from the other chemotherapeutic drugs, including two cases of mild (grades 1 and 2) peripheral neuropathy [103]. Finally, a phase I study that followed its patients for 24 months examined the use of bortezomib in addition to ifosfamide, carboplatin, and etoposide for relapsed and refractory Hodgkin's lymphoma in young adults aged 21-39 years. The regimen was well-tolerated, with no dose-limiting toxicities and no peripheral neuropathy [104]. Therefore, although younger patients may be spared the peripheral neuropathy observed in adults, studies have been limited and brief in general, so it remains important to monitor the use of bortezomib for this neurotoxicity.

Poly-(adenosine-diphosphate-ribose)-polymerase inhibitors—Agents that inhibit the base excision repair enzyme poly-(adenosine-diphosphate-ribose)-polymerase are being used to attempt to interfere with cancer DNA repair and potentiate chemotherapy and radiotherapy. The first clinical trial of a poly-(adenosine-diphosphate-ribose)-polymerase inhibitor, AG014699, combined with temozolomide in 33 adults with advanced malignancy, demonstrated no dose-limiting toxicity (including neurotoxicity) attributable to the medication up to 18 mg/m^2/day [105]. Another poly-(adenosine-diphosphate-ribose)-polymerase inhibitor, olaparib (AZD2281, AstraZeneca), was combined with topotecan in a phase I study of 21 adults with advanced noncentral nervous system tumors, and demonstrated significant dose-limiting hematologic toxicity, but no neurotoxicity [106]. The intravenous poly-(adenosine-diphosphate-ribose)-polymerase inhibitor AG014699 exhibited no serious neurotoxicity when tested with temozolomide. Another intravenous poly-(adenosinediphosphate-ribose)-polymerase inhibitor, BSI-201, has been used as a single agent and in phase I trials with topotecan, gemcitabine, temozolomide, or carboplatin/paclitaxel, also with no serious neurotoxicity reported [107]. A large number of ongoing trials of the poly-(adenosine-diphosphate-ribose)-polymerase inhibitor ABT-888 have been undertaken, but at this time, no clinical toxicity data are available. Notably, preclinical data suggest that poly-(adenosine-diphosphate-ribose)-polymerase regulation may provide neuroprotection in neurodegenerative diseases such as Parkinson disease and in neurotoxicity-induced neuronal damage, probably attributable to the inhibition of neuronal apoptosis, the suppression of inflammation, and the activation of cell survival signaling [108].

Conclusion

The recent understanding of cancer's molecular pathogenesis has led to the development of biologically targeted drugs with the potential to overcome tumor development, progression, and resistance to conventional therapies. The goals of cancer treatment with these agents are twofold: (1) to treat tumors more effectively that have been resistant to traditional chemotherapy, and (2) to inflict less harm on normal tissue, including the developing nervous system. To date, the neurotoxicity of molecularly targeted agents has been relatively limited. However, long-term follow-up data are lacking, and these agents may not enable us to evade the late neurologic effects observed with traditional chemotherapies. In addition, effective therapies for currently resistant cancers will likely require multiple biologic agents to prevail over escape pathways and other mechanisms by which tumors can continue to

proliferate. Combination treatments may cause synergistic anticancer effects, but may also increase the likelihood of adverse events, including neurotoxicity.

Biologically targeted agents are directed at molecular pathways that are important in controlling both tumorigenesis and developmental processes. Therefore, when used in pediatric patients, they may cause neurotoxicity and adverse neurologic sequelae that have not been evident in adults. Preclinical studies considered the effects of these agents on neural precursor cells. One example involves the study already described, demonstrating cognitive deficits in γ-secretase knockout mice. Another recent study indicated that erlotinib and bortezomib exerted less toxic effects on neural stem/progenitor cells in culture, compared with the traditional chemotherapeutic agents temozolomide and cis-platin [109]. This finding is encouraging, especially considering the important role of neural stem/progenitor cells in brain development, learning, and memory. However, the authors speculated that the preferential toxicity of erlotinib for glial stem cells over neural stem cells might occur because neural stem/progenitor cells express surface epidermal growth factor receptors only at certain developmental stages. If this theory is correct, the pediatric brain may not have the same protection, and may be more vulnerable to toxicity compared with the adult brain. The effects of newer targeted agents on the developing nervous system must be further investigated, both preclinically and in longitudinal trials in children.

Future research on molecularly targeted agents must include additional preclinical investigations of neurotoxicity during development, as well as close monitoring during clinical trials, using thorough neurologic examinations, neurocognitive testing, and neuroimaging. While the efficacy of these agents is being explored (both as monotherapy and in rational combinations), the close monitoring of neurologic and neurocognitive side effects and subsequent modifications to research protocols will hopefully advance the goal of curing more patients of pediatric cancer, with fewer long-term adverse effects. In addition, the recognition and early detection of neurotoxicity and adverse neurologic sequelae by clinicians may lead to interventions that improve functional outcomes.

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Table 1

Neurotoxicities reported to be associated with biologically targeted agents

Class	Drug	Neurotoxicity
EGFR inhibitors	Erlotinib	Worsening of peripheral neuropathy from other agents
	Gefitinib	Intratumoral hemorrhage
PDGF inhibitors	Imatinib	Intratumoral hemorrhage, myalgias, muscle cramping, possible growth impairment
VEGF inhibitors	Bevacizumab	Bleeding, cerebrovascular events, PRES, radiation necrosis
Farnesyltransferase inhibitors	Tipifarnib	Peripheral neuropathy, headache, dizziness (all rare in children)
Raf inhibitors	Sunitinib and sorefenib	PRES, cerebrovascular events
mTOR inhibitors	Sirolimus	PRES, cerebrovascular events
Antiangiogenetic	Thalidomide	Peripheral neuropathy
Histone deactylase inhibitors	Suberoylanilide hydroxamic acid	Fatigue
	Valproic acid (Depakote)	Somnolence
Proteasome inhibitors	Bortezomib	Peripheral neuropathy

Abbreviations:

EGFR = Epidermal growth factor receptor

mTOR = Mammalian target of rapamycin

PDGF = Platelet-derived growth factor

PRES = Posterior reversible encephalopathy syndrome

VEGF = Vascular endothelial growth factor

Table 2

Neurotoxicities in pediatric clinical trials of biologic agents targeting receptor tyrosine kinases and downstream signal transduction pathways, including all published Children's Oncology Group and Pediatric Brain Tumor Consortium trials

Class	Drug	Trial	Phase	Study Population	Number of Patients	Neurotoxicity
EGFR inhibitors	Erlotinib (Tarceva)	COG-ADVL0214 [5]	I	Solid tumors	46	None
		SJHGO4 [6]	I	HGG	25	None
		ITCC trial [7]	I	BSG, other BT	51	Intratumoral hemorrhage
	Gefitinib (Iressa)	COG-ADVL0016 [12]	I	Solid tumors	25	Intratumoral hemorrhage
		PBTC-007 [13]	I	BSG, HGG	20	Intratumoral hemorrhage
		ZD1839 [14]	I	Solid tumors	29	None
		PBTC-00715	II	BSG, HGG	44	Intratumoral hemorrhage
	Lapatinib (Tykerb)	PBTC-016 [17]	I	Refractory CNS	59	None
PGFR inhibitors	Imatinib (Gleevac)	COG-AALL0031 [20]	I	Ph + ALL	15	None
		COG-AAML0123 [21]	I	Ph + AML	31	None
		PBTC-006 [22]	I	BSG, HGG	27	Intratumoral hemorrhage
VEGF inhibitors	Bevacizumab (Avastin)	PBTC-022 [42]	II	HGG, BSG	31	None
Farnesyltransferase inhibitors	Tipifarnib (Zarnestra)	COG-ADVL0116 [50]	I	Leukemia	29	Rare headache, dizziness
		PBTC-014 [51]	I	BSG	17	Microhemorrhages, Klüver-Bucy syndrome
		COG-ACNS0226 [53]	II	HGG, PNET, BSG	91	Rare motor neuropathy Seizure, headache, altered mental status
Raf inhibitors	Sunitinib (Sutent)	COG-ADVL0612 [30]	I	Solid tumors	23	Fatigue

Abbreviations:

AALL = Adolescents with acute lymphoblastic leukemia

AAML = Adolescents with acute myelogenous leukemia

ADVL = Adolescents with refractory leukemias

BSG = Brainstem glioma

BT = Brain tumor

CML = Chronic myelogenous leukemia

COG = Children's Oncology Group

CNS = Central nervous system

EGFR = Epidermal growth factor receptor

GBM = Glioblastoma

HGG = High-grade glioma

ITCC = Innovative Therapies for Children With Cancer

PBTC = Pediatric Brain Tumor Consortium

Ph+ ALL = Philadelphia chromosome positive acute lymphoblastic leukemia

Ph+ AML = Philadelphia chromosome positive acute myelogenous leukema

VEGF = Vascular endothelial growth factor