

Emerging treatment options for the treatment of neuroblastoma: potential role of perifosine

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Abstract: Achieving a cure for high-risk neuroblastoma, the most common extracranial solid tumor in children, remains a formidable task despite the recent addition of antibody-mediated anti-GD2 immunotherapy to established multimodality therapy. The PI3K/Akt pathway is a pivotal signaling pathway utilized by a plethora of receptor tyrosine kinases that contribute to the aggressive phenotype of high-risk neuroblastoma. Akt is aberrantly activated in high-risk neuroblastoma and is therefore an attractive therapeutic target. Perifosine is the best-characterized Akt inhibitor in preclinical studies and in clinical trials in adults, although safety in children is not yet confirmed. It is a synthetic third-generation alkylphospholipid with good oral bioavailability and modest side effects. Perifosine targets the lipid-binding PH domain of Akt and inhibits the translocation of Akt to the cell membrane, an essential step for Akt activation. It decreases Akt phosphorylation and increases caspase-dependent apoptosis in neuroblastoma cell lines, inhibits growth of neuroblastoma xenografts, and overcomes RTK/ligand-mediated chemoresistance. It is currently being studied in two Phase I clinical trials in children with recurrent or refractory solid tumors including neuroblastoma. In the single agent trial (ClinicalTrials.gov identifier NCT00776867), maximum tolerated dose has not yet been reached and pharmacokinetic data has been accrued. In the second study (ClinicalTrials.gov identifier NCT01049841), patients are treated with a combination of perifosine and the mTOR-inhibitor temsirolimus based on preclinical data showing synergy of the two agents, and the premise that direct Akt inhibition may overcome Akt activation secondary to mTOR inhibition. Based on results from adult trials, it is unlikely that perifosine alone will produce dramatic therapeutic effects against high-risk neuroblastoma. However, given the recent encouraging early-phase combination therapy results in adults with multiple myeloma and colorectal carcinoma, rational perifosine-containing combination regimens hold promise for neuroblastoma therapy. These will be explored after safety in children is established in Phase I studies.

Keywords: neuroblastoma, Akt pathway, perifosine

Introduction

Curing neuroblastoma, the most frequent pediatric solid tumor outside the central nervous system, remains a challenge. Although it accounts for approximately 7% of malignancies in patients younger than 15 years, neuroblastoma accounts for 15% of all pediatric oncology deaths.¹ Neuroblastoma arises from the neural crest cells of the sympathetic nervous system, and exhibits a diverse clinical picture. Infants may experience complete regression of the disease without any therapy; and cytotoxic therapy can be withheld for most patients with locoregional disease. However, most patients have metastatic disease at diagnosis, and the prognosis for those diagnosed >18 months of age or those with *MYCN*-amplified disease is poor despite aggressive multimodality therapy.

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Tumors initially respond to intensive chemotherapy, surgery, and radiotherapy; however most patients relapse and become resistant to chemotherapy.² Disialoganglioside (GD2) has thus far been the most-frequently targeted tumor antigen on neuroblastoma.³ Antibody-based anti-GD2 immunotherapy with or without myeloablative therapy and autologous stem cell transplant has shown encouraging results with significantly improved short-term survival.^{4,5} However, currently, long-term event-free survival for patients diagnosed with high-risk disease (which constitute the majority of neuroblastoma cases) as reported in multi-center studies is <40%.⁶⁻⁹ Patients with recurrent neuroblastoma have a far worse outcome.¹⁰ Early tumor detection by screening did not reduce tumor-related mortality.^{11,12} Therefore, new therapeutic strategies are needed to improve the outcome.

Advances in our understanding of the biology of neuroblastoma have given us insights in identifying neuroblastoma-specific molecular targets for novel therapy. Certain genetic alterations are associated with more aggressive phenotype and high-risk disease. These include *MYCN*-amplification, 1p deletion, loss of heterozygosity at chromosome 11q, and 17q gain.¹³ However, corresponding viable targetable molecules for therapy have not been identified. Recently, mutations and amplifications of anaplastic lymphoma kinase (ALK) have been described in small subsets of patients of neuroblastoma.¹⁴⁻¹⁶ This has led to the hope that ALK inhibitors may provide effective therapeutic options for patients with neuroblastoma, and early phase studies are underway. In addition, high-risk neuroblastoma is associated with elevated expression of the neurotrophin-receptor tropomyosin receptor kinase TrkB which is considered to act as an oncogenic kinase in a subset of patients.¹⁷ A safe and biologically effective dose of the multi-kinase inhibitor lestaurtinib which has anti-TrkB activity has recently been established, though single agent activity against neuroblastoma is modest.^{18,19} TrkB activates the downstream phosphatidylinositol 3'-kinase (PI3K)/Akt pathway as do a plethora of other receptor tyrosine kinases (RTKs) implicated in neuroblastoma pathogenesis and behavior.^{20,21} Therefore Akt inhibition may be therapeutically effective for high-risk neuroblastoma. In this review, we focus on the role of the Akt pathway in neuroblastoma and specifically, a possible therapeutic role for the Akt inhibitor perifosine.

PI3K/Akt signaling pathway

The PI3K/Akt pathway is a key signaling pathway that contributes to cell growth, proliferation, survival, angiogenesis, and glucose metabolism.²²⁻²⁴ Upon growth

factor binding, transmembrane RTKs are activated by phosphorylation that in turn activates PI3K.²⁵ Activation of PI3K generates phosphatidylinositol-3,4,5-trisphosphate (PIP3) which then anchors the serine/threonine kinase Akt to the plasma membrane via the binding of PIP3 to the pleckstrin homology (PH) domain of Akt.²⁶ The binding triggers a conformational change of Akt and releases the autoinhibition function of the PH domain. This results in the exposure of the two crucial amino acid sites: threonine 308 (Thr308) in the activation loop of the kinase; and serine 473 (Ser473) at the C-terminus for phosphorylation. Activation of Akt requires both translocation to the plasma membrane and phosphorylation of the two key residues by phosphoinositide-dependent kinase (PDK)-1 and PDK-2.²⁷ Once activated, Akt dissociates from the plasma membrane and moves to various cellular compartments and targets downstream substrates including mammalian target of rapamycin (mTOR) pathway.^{22,28} A key negative regulator of Akt signaling is the tumor suppressor gene phosphatase and tensin homolog (PTEN). PTEN can dephosphorylate PIP3 and thereby inhibit PI3K/Akt signaling.²⁸ This pathway is also negatively regulated by protein serine/threonine phosphatase which specifically dephosphorylates Ser473.^{22,29,30} (Figure 1).

PI3K/Akt pathway and neuroblastoma

Aberrant activation of the Akt pathway has been widely implicated in many cancers.³¹ It is one of the most frequently involved pathways in sporadic human tumors, with estimates suggesting that mutation in one or another PI3K/Akt pathway component accounts for up to 30% of all human cancers.^{23,32} Conversely PTEN is considered to be a major tumor suppressor.³³ In one study, tissue microarray analysis revealed phosphorylation of Akt at Ser473 and Thr308 in 57% of primary neuroblastoma samples tested. Activation was highly correlated with the phosphorylation of S6 ribosomal protein, a downstream target of mTOR pathway. Activation of the Akt pathway correlated with several parameters of aggressive disease, including *MYCN* amplification, chromosome 1p aberrations, advanced disease stage, older age at diagnosis, and unfavorable histology.³⁴ Phosphorylation of Akt correlated with decreased event-free or overall survival of neuroblastoma patients, but S6 or extracellular signal-regulated kinase (ERK) phosphorylation did not.³⁴ Another group studied 39 high-risk neuroblastoma samples using phospho-antibodies specifically for the phosphorylated proteins in PI3K/AKT pathways. It was found that most of

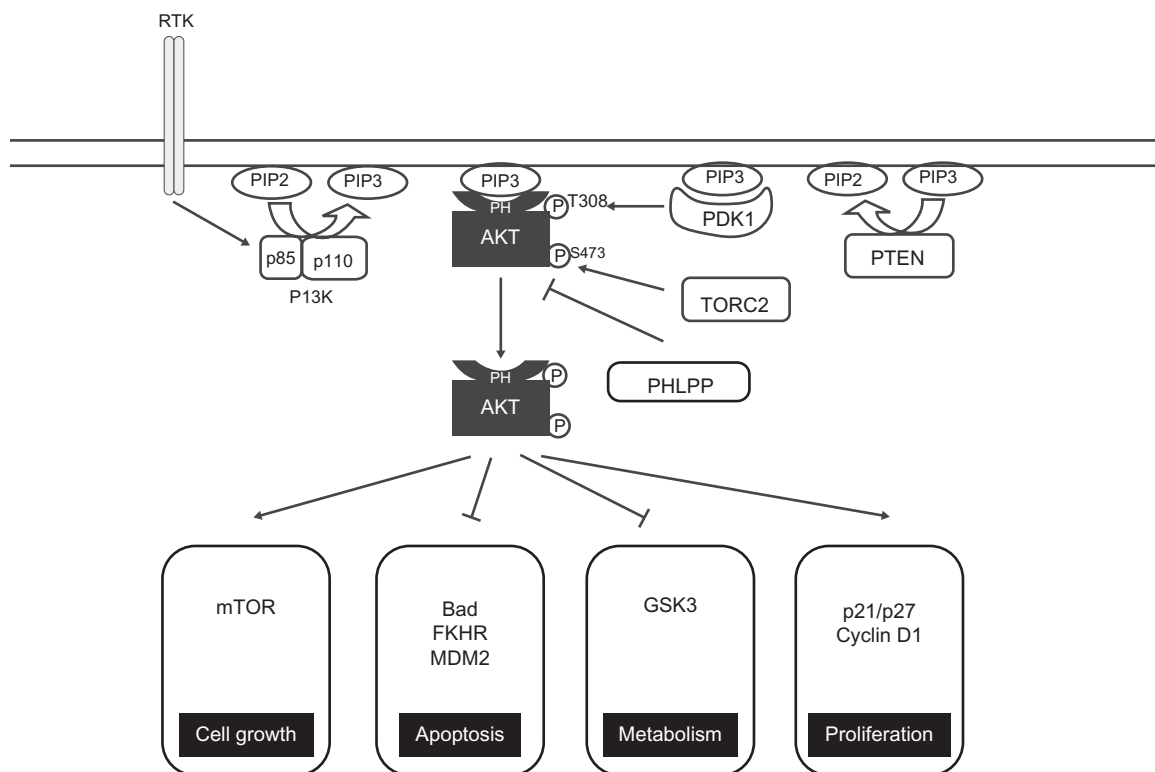


Figure 1 Diagrammatic representation of the Akt signaling pathway.

Notes: Activation of receptor tyrosine kinase (RTK) by growth factor binding activates PI3K. Activated PI3K phosphorylates PIP2 and generates PIP3, a reaction that can be reversed by PTEN. The PH domain of Akt binds to PIP3, which then triggers a conformational change of Akt that results in the phosphorylation of two critical amino acids, Thr308 and Ser473 by PDK-1 and TORC2 respectively. The phosphorylated Akt then dissociates from the plasma membrane and targets downstream pathways including cell growth, survival, proliferation, and metabolism. Besides PTEN, this pathway is also negatively regulated by PHLPP, a protein serine/threonine phosphatase that can dephosphorylate Ser473 of Akt.

Abbreviations: PIP2, Phosphatidylinositol (4,5)-bisphosphate; PIP3, Phosphatidylinositol (3,4,5)-trisphosphate; PDK1, 3-Phosphoinositide-dependent protein kinase 1; TORC2, mammalian target of rapamycin complex 2; PTEN, Phosphatase and tensin homolog; PHLPP, PH domain and Leucine rich repeat protein phosphatases; mTOR, mammalian target of rapamycin Bad, Bcl-xL/Bcl-2-associated death promoter; FKHR, Forkhead transcription factors; MDM2, mouse double minute 2; GSK3, glycogen synthase kinase 3.

the tumors were positive for PI3Kp85 and PI3Kp110, as well as for phosphorylated Akt, mTOR, and S6.³⁵ In another study, expression of activated Akt and mTOR was detected in all 34 primary neuroblastoma tissue samples tested, but not in non-malignant adrenal medullas.³⁶ Lower levels of Akt activation were detected in low-risk neuroblastoma (tumors expected to mature or regress spontaneously) detected by mass screening when compared to classical neuroblastoma.³⁷ In vitro studies suggest that the PI3K/Akt plays a key role in neuroblastoma cell survival mediated by RTK ligands/RTKs including TrkB/brain-derived neurotrophic factor (BDNF),³⁸ insulin-like growth factor (IGF)/IGF-receptor,^{39,40} epidermal growth factor (EGF)/EGF-receptor,^{41,42} platelet-derived growth factor (PDGF)/PDGF-receptor,⁴³ and vascular endothelial growth factor (VEGF)/VEGF-receptor.^{44–46} Several studies also indicate that Akt is involved in controlling apoptosis in neuroblastoma cells through caspase-dependent and caspase-independent mechanisms,^{47,48} in protein synthesis and cell growth via downstream mTOR signaling,⁴⁹ and in cell cycle control via interaction with

glycogen synthase kinase-3 β (GSK3).^{50,51} Recently, Akt regulation in neuroblastoma cells has been linked to the micro RNAs miR-149⁵² and miR-184.⁵³ Activation of the Akt pathway in neuroblastoma can be caused by mutation or overexpression of RTKs and/or their ligands. Besides the above growth factors/receptors, activating ALK mutations have been shown to enhance Akt activity.^{16,54,55} The Akt pathway can also be aberrantly activated by inactivation of tumor suppressor PTEN by homozygous deletion or promoter hypermethylation.^{56,57} In addition, several other proteins can influence Akt activation or inhibition in neuroblastoma. These include TNF-related apoptosis inducing ligand (TRAIL),⁵⁸ PKC family proteins,⁵⁹ and FOXO3a.⁶⁰ In summary, based on current studies, Akt is aberrantly activated in a majority of high-risk neuroblastic tumors, and appears to be an important mediator of the cancer phenotype in neuroblastoma. However, unlike in some adult cancers, Akt/PI3K mutations have not been detected in neuroblastoma including in a high-throughput sequenom-based analysis of a large number of primary tumors.⁶¹

Targeting the Akt pathway

Recent attention has been focused on the concept of “oncogene addiction,” which hypothesizes that cancer cells are dependent on, or “addicted” to, one or a few genes for both maintenance and survival of the malignant cells.⁶² Therefore, inhibiting only one or a few of these abnormalities may inhibit cancer cell growth and translate to improved outcome. Because Akt is at the pivotal nodal point in the signaling pathway of a majority of RTKs, and the activation of the Akt pathway has been frequently found in cancers, it is an attractive target for novel anticancer drugs. If Akt is inhibited, the survival signaling of most RTKs will be blocked, obviating the need to identify tumor-specific “drug-able” genetic/epigenetic changes or patient tumor-specific RTKs. Substrates downstream of Akt critical for cell survival can be cell type specific, and inhibition of individual substrates may miss key targets that are responsible for cell survival and proliferation. Directly targeting Akt can circumvent feedback activation of Akt that has been observed with mTOR inhibition.^{22,69} Therefore, direct targeting of Akt, especially in tumors with an activated Akt pathway such as neuroblastoma, has the potential to be therapeutically effective. Various strategies have been used to develop Akt inhibitors, including screening small molecules that target the ATP-binding domain or the PH domain of Akt, and designing peptides that model the interaction of Akt with inhibitory binding proteins.^{63,68,69} Several Akt inhibitors are in early phase clinical trials for a variety of cancers.⁶⁴ Perifosine is the most well characterized and clinically evaluated Akt inhibitor thus far.

Perifosine: an anticancer Akt inhibitor

Perifosine is a synthetic oral alkylphospholipid with a piperidine head group. It is a third generation anti-tumor alkylphospholipid analog related to miltefosine and edelfosine, but with better oral availability and fewer gastrointestinal side effects.⁶⁵ The synthetic alkylphospholipids are membrane-permeable ether lipids that are easily inserted into the outer leaflet of the plasma membrane and subsequently induce profound biological changes and ultimately lead to cell death.^{63,66,68,69} Perifosine targets the lipid-binding PH domain of Akt and inhibits the translocation of Akt to the cell membrane, an essential step for the activation of Akt.⁶⁷⁻⁷⁰ Perifosine has also been shown to inhibit MAPK⁷¹ and JNK⁷² pathways. In vitro, perifosine inhibits Akt at low micromolar concentrations and causes apoptosis in many human cancers including multiple myeloma, T-acute lymphoblastic leukemia, acute myeloid leukemia, non-small cell lung carcinoma,

prostate carcinoma, hepatocellular carcinoma, ovarian carcinoma, and medulloblastoma.⁷²⁻⁸⁰ In vivo, Akt inhibition by perifosine has been documented in xenograft mouse models of multiple myeloma,⁸¹⁻⁸³ glioma,⁸⁴ Waldenstrom’s macroglobulinemia,⁸⁵ breast, ovarian, and prostate cancer.⁸⁶ Cell lines with activating Akt pathways are more sensitive to perifosine in vitro than those without, and the ability of perifosine to inhibit tumor in vivo is correlated with the decreases in phosphorylation of Akt and other components of the pathway in the tumor.⁸⁶ In pediatric tumors other than neuroblastoma, perifosine-induced Akt inhibition has been demonstrated in a brainstem glioma mouse model,⁸⁷ and it was shown to act as a radiation-sensitizer in murine medulloblastoma.⁸⁸

Perifosine has been tested in several clinical trials in adults with various tumor types. In Phase I studies, the maximum-tolerated dose was determined to be 150 mg orally for each of the four loading doses on day 1 followed by 100 mg orally once daily as maintenance.⁸⁹ The maximum tolerated maintenance daily dose of perifosine was 200 mg/day,⁹⁰ and the half-life was estimated to be about 4 days.⁹¹ Perifosine was well tolerated in general, with common toxicities being gastrointestinal symptoms and fatigue. Toxicities were less than grade 3 in the majority of patients. Bone marrow suppression was minor.^{89,90} Multiple adult Phase II trials using perifosine in various solid tumor and sarcomas have been completed. Single agent anti-tumor activity was modest and was noted against sarcoma,⁹² Waldenstrom’s macroglobulinemia,⁹³ renal cell carcinoma, and non-small cell lung cancer.⁶⁴ A randomized placebo-controlled Phase II study comparing perifosine plus capecitabine to capecitabine alone as second or third-line therapy in patients with metastatic colorectal carcinoma showed significantly better time to progression and overall survival for patients treated with the combination.⁹⁴ Similarly, the combination of perifosine plus bortezomib and dexamethasone demonstrated encouraging activity in pretreated bortezomib-exposed patients with resistant multiple myeloma.⁹⁵ Phase III studies have now been initiated for both colorectal cancer and for multiple myeloma.

Perifosine: preclinical studies in neuroblastoma

Constitutively activated Akt has been detected in neuroblastoma cell lines and increases cell survival;³⁸ in primary tumors. It is associated with high-risk disease.³⁴

Activation of neuroblastoma RTKs can increase Akt activation and mediate chemoresistance, warranting consideration of Akt as a tumor target for therapy.

Perifosine in μM concentrations decreased Akt phosphorylation and increased caspase-dependent apoptosis in four different neuroblastoma cell lines bearing different genetic and biological characteristics resembling a spectrum of high-risk neuroblastoma.⁹⁶ In xenograft models, perifosine inhibited the growth of neuroblastoma tumors with an improved survival of perifosine-treated mice with minimal toxicity. Xenografts in perifosine-treated mice showed inhibition of Akt activation and induction of caspase-dependent apoptosis.⁹⁶ Interestingly, neuroblastoma cell lines with both wild-type and mutant ALK were sensitive to perifosine. The role of perifosine in overcoming chemoresistance was tested in a TrkB-expressing neuroblastoma cell line TB3 which demonstrates BDNF-induced Akt activation. Pre-treatment with perifosine blocked brain-derived neurotrophic factor (BDNF)/TrkB-induced TrkB phosphorylation and attenuated BDNF-mediated etoposide chemoresistance in vitro. In mice bearing TB3 xenografts, the combination of perifosine and etoposide reduced tumor growth significantly when compared to treatment with either drug alone, suggesting a role for perifosine in overcoming chemoresistance mediated by Akt-activation.⁹⁷

Rationale for combination strategies with perifosine

The results of Phase II trials using perifosine as a single agent are modest.⁶⁴ However, data from perifosine-including combination therapies for multiple myeloma and colorectal cancer are encouraging.^{94,95} It is likely that cancers depend on more than one pathway for their proliferation and survival and inhibitors of a single deregulated pathway may be insufficient to induce cell death. Indeed in vitro, perifosine has been shown to have a synergistic antitumor effect when combined with various biological agents including UCN-01,⁹⁸ histone deacetylase inhibitors,⁹⁹ TRAIL,^{73,100} erlotinib,⁷⁵ cetuximab,⁷¹ and 17-DMAG.¹⁰¹ In particular, simultaneous targeting of the Akt pathway by perifosine and mTOR inhibition induced cell death and decreased proliferation in murine glioblastoma studies.¹⁰² In addition, perifosine synergizes with conventional chemotherapy agents against multiple myeloma,⁸² endometrial cancer,¹⁰³ and acute myeloid leukemia.¹⁰⁴ In murine medulloblastoma and brain stem glioma model, perifosine has been shown to sensitize tumor cells to radiation therapy.^{88,105} Taken together, these preclinical data suggest that combination therapy can increase the cytotoxic effect of perifosine, and Akt inhibition can sensitize the responsiveness of tumor cells to chemotherapy and radiation therapy. In preclinical studies of TrkB-expressing

neuroblastoma xenografts, both perifosine and lestaurtinib¹⁰⁶ synergize with chemotherapy, suggesting that TrkB-mediated chemoresistance can be overcome by inhibition of RTK-driven survival pathways. Since perifosine has little bone marrow toxicity, combination conventional chemotherapy with perifosine could lead to being more effective in tumor killing without major myelosuppression.

Perifosine: clinical studies in neuroblastoma

Perifosine is currently being tested in two ongoing pediatric Phase I studies, both being conducted at Memorial Sloan-Kettering Cancer Center. The first is a Phase I dose escalation study of perifosine as a single agent for recurrent pediatric solid tumors including neuroblastoma (ClinicalTrials.gov identifier number NCT00776867). This has a standard Phase I design to determine the maximal tolerated dose (MTD) of perifosine in children. Given the restrictions of perifosine oral formulation (only available in 50 mg tablets), the drug is not dosed per surface area, but in five groups where grouping is based on body surface area. All patients receive an oral load on day 1 (50–300 mg) followed by maintenance doses (50–200 mg) ranging from once every 4 days to once daily. This corresponds to an initial dose level of approximately 25 mg/m²/day with increments of 25 mg/m²/day per dose level. Perifosine is a potential substrate for the cytochrome P450 system which is induced by enzyme inducing anti-epileptic drugs; hence, patients are not allowed to receive the latter concurrently with perifosine. Dose-limiting toxicities monitored for include any non-hematological toxicity \geq grade 3 and severe myelosuppression. Secondary objectives include assessment of perifosine pharmacokinetics and correlation of molecular features of tumors with response, if any. Preliminary data were reported on nine patients (including two patients with neuroblastoma) treated at the first three dose levels. No dose-limiting toxicities were reported and MTD has not yet been reached. Grade 2 toxicities possibly related to perifosine included asthenia (22%), asymptomatic hepatic transaminase elevation (22%), neutropenia (33%), leukopenia (11%), hyperglycemia (22%), hypomagnesemia (22%), hypophosphatemia (11%), and colitis which resolved despite drug continuation (11%). Preliminary pharmacokinetic data resulted in the following steady state serum levels: 14.1 \pm 4 μM for dose level 1, 32.8 \pm 8.1 μM for dose level 2, and 31.6 \pm 7.8 μM for dose level 3.¹⁰⁷ Both patients did not show disease progression at 9+ months on therapy.¹⁰⁸ Given the excellent safety profile observed at the third dose level, additional patients with neuroblastoma have been treated

at dose level 3 for a preliminary evaluation of efficacy of perifosine monotherapy against neuroblastoma. To date, an additional twelve patients with neuroblastoma have been treated on the protocol.

The second study investigates the combination of perifosine and temsirolimus in a Phase I clinical trial for patients with recurrent pediatric solid tumors (ClinicalTrials.gov identifier number NCT01049841). It seeks to build on the hypothesis that Akt inhibition by perifosine, in conjunction with disruption of the downstream mTOR pathway by the rapamycin analog temsirolimus, can have a synergistic anti-tumor effect. Akt targeting with perifosine can potentially circumvent the activation of Akt observed with mTOR inhibition.¹⁰⁹ Furthermore, with the exception of gastrointestinal side effects, the two drugs have non-overlapping toxicities, possibly allowing therapeutic use in combination without major toxicity. The MTD of temsirolimus as a single agent in children was determined to be 150 mg/m²/dose weekly intravenously¹¹⁰ but a dose of 75 mg/m²/day has been adopted for Phase II pediatric studies.¹¹¹ The primary objective is to determine the maximum tolerated doses of perifosine and temsirolimus when used in combination. A dosing strategy similar to that used for the single agent perifosine study is used for daily oral perifosine dosing. Temsirolimus is first escalated from 25 to 75 mg/m² IV every 4 weeks with perifosine escalation in three cohorts after the final dose of temsirolimus is reached. Secondary objectives include measurement of perifosine and temsirolimus pharmacokinetics and acquiring preliminary data regarding efficacy of the combination. The design of further clinical trials using perifosine in pediatrics will likely be predicated on the establishment of perifosine MTD in the above two studies.

Conclusion

Clinical and laboratory research over the last several decades has made considerable progress in understanding the biology and improving the therapy of neuroblastoma. However, the long-term survival rate for the high-risk patients remains <40%. Therapy aimed at newer therapeutic targets should therefore be explored. Akt has a potentially pivotal role in mediating RTK signaling in neuroblastoma. The Akt pathway is activated in the majority of neuroblastoma and is associated with a poor prognosis. Preclinical data suggests that perifosine, an Akt inhibitor, is an effective therapeutic agent with tolerable toxicity. Ongoing Phase I pediatric studies will establish the safety profile for this agent in children, but lessons learned from perifosine

trials in adults suggest that the single agent perifosine is unlikely to yield impressive therapeutic results. Based on an understanding of its underlying mechanism of action, recent preclinical data from neuroblastoma cell lines and xenograft studies, and encouraging clinical data from early phase studies in adult cancers, perifosine in combination with other novel agents or established chemotherapy has the potential to add to the increasing armamentarium of therapies being developed for the treatment of high-risk neuroblastoma.

Disclosure

The authors report no conflicts of interest in this work.

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