Neuroblastoma is one of the most common and deadly forms of childhood cancer. The tumors generally arise in the abdomen (especially adrenal medulla) or chest, and they are characterized by biological and clinical heterogeneity (1). Neuroblastomas may regress spontaneously in an infant or mature into a benign ganglioneuroma in an older patient. However, most children older than 12–18 months at diagnosis have unreactable or metastatic disease, and unfortunately, the majority of these children die, despite aggressive multimodality therapy (2–4). Furthermore, there is considerable long-term morbidity in the survivors. Therefore, more effective and less toxic therapy is needed for these patients. Fortunately, insights into the genes, proteins, and pathways important for neuroblastoma pathogenesis have provided some targets for future therapy (3,5,6).

Several receptor tyrosine kinases (RTKs) have been identified that play important roles in neuroblastoma behavior, such as growth, differentiation, or death. These include the NTRK family of neurotrophin receptors (7,8). Biologically favorable tumors are characterized by near-triploid DNA content, a lack of unfavorable structural changes in the chromosomes (see below), and high expression of TrkA (NTRK1). These tumors are prone to spontaneous regression or differentiation, and TrkA may contribute to this behavior (9–13). Conversely, biologically unfavorable tumors are characterized by MYCN amplification, deletions of chromosome 1p36 or 11q23, as well as coexpression of TrkB (NTRK2) and its ligand, the brain-derived neurotrophic factor (BDNF), resulting in activation of an autocrine (or paracrine) survival pathway (14,15,16–20). The anaplastic lymphoma receptor tyrosine kinase, ALK, has been identified as the gene responsible for most familial neuroblastomas and may contribute to sporadic disease in a small subset of neuroblastoma patients (21–24). Other RTKs that have been implicated in neuroblastoma pathogenesis or behavior include RET (REarranged during Transfection) (25–27), the epidermal growth factor receptor (EGFR) (28–30), the insulin-like growth factor receptor (IGF1R) (31,32), and vascular endothelial growth factor receptors (VEGFRs) (33,34). Indeed, several preclinical studies have been done with therapeutic agents targeting these RTKs, and some of these agents have also been tested in clinical trials of neuroblastoma (29,33,35–39).

In this issue of the Journal, Li et al. (40) conduct both in vitro and in vivo preclinical testing of the AKT (protein kinase B) inhibitor perifosine. AKT, a serine–threonine kinase, is at a pivotal nodal point in the signaling pathway of almost all RTKs and is activated by the phosphoinositol-3-kinase. AKT activates a myriad of signaling pathways, most notably the mammalian target of rapamycin (mTOR) pathway that is involved in cell proliferation and survival (41). However, the specific pathways activated, and the consequences on cell survival, growth, differentiation, or death depend on the particular cell type and the state of maturation. From the tumor treatment perspective, targeting the AKT pathway would be advantageous because it should be effective in blocking critical survival signaling of most RTKs. Therefore, it would not be necessary to know if a given tumor relied on a specific RTK, as long as its survival and/or other malignant characteristics (such as invasion, metastasis, drug resistance, and angiogenesis) were dependent on at least one RTK. From the patient perspective, targeting such a generic pathway could be problematic in terms of systemic toxicity. This has been not just a theoretical concern but a real problem with several AKT inhibitors that have reached clinical trials (42,43).

Based on the preliminary data presented in this report (40), perifosine is effective at inhibiting the in vitro growth of four human neuroblastoma cell lines with genetic and biological characteristics representing a spectrum of high-risk neuroblastomas. Cells appear to die by a caspase-dependent apoptotic mechanism. Furthermore, it causes regression or at least inhibition of growth of the neuroblastoma lines growing as xenografts, and it appears to be relatively nontoxic. Perifosine was able to inhibit the growth of tumors with either wild-type or mutant tumor protein p53 (TP53), so it clearly works by mechanisms independent of p53-regulated pathways. Previous studies have shown that ALK activation by amplification, overexpression, or mutation has been detected in a subset of aggressive neuroblastomas, but some ALK mutations confer resistance against ALK inhibitors (21–24). Because AKT is a downstream signaling target of activated ALK, it was logical to determine if neuroblastomas expressing ALK could be inhibited by perifosine. The authors used neuroblastoma cell lines with both wild-type and mutant ALK in this study (40), and both were sensitive to perifosine, suggesting that the resistance conferred by ALK mutations did not extend to inhibition of critical downstream signaling pathways.

Perifosine was only tested as a single agent in this study (40), but others have combined perifosine with agents such as bortezomib (proteosome inhibitor), rapamycin (mTOR inhibitor), or other agents used to treat multiple hematopoietic malignancies and observed additive or synergistic effects (44–47). Thus, perifosine not only demonstrates efficacy as a single agent but can also enhance the effect of a variety of other agents working by different mechanisms. Indeed, we (35,36,38) and others have shown that coadministration of an RTK inhibitor with conventional chemotherapy significantly enhances the antitumor effect over either agent alone. This suggests that the removal of an important RTK-driven survival pathway makes the tumor cells more sensitive to cytotoxic drugs.
In summary, this article suggests that perfosine (or potentially other agents targeting the phosphoinositid-3-kinase-AKT signaling) is an effective and relatively nontoxic agent for the treatment of neuroblastomas and perhaps other cancers that rely on this signaling pathway for their survival. Its disadvantage is that it is not as selective for a specific RTK, so there may be unintended toxic effects. However, from the cancer treatment perspective, this lack of specificity is an advantage because it could be used to target neuroblastomas that depend on one or more RTKs (eg, TrkB, ALK, RET, EGFR, IGF1R, VEGFRs) for their survival. Certainly, the results warrant further investigation of this agent alone, but particularly in combination with other agents. Perfosine is already in clinical trials in adults (48–52), so perhaps it is time for pediatric oncologists to get “into the AKT” and consider treating neuroblastomas or other RTK-dependent cancers with this seemingly effective and relatively nontoxic agent.

References


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