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Potential Therapies for Anaplastic Lymphoma Kinase-Driven Tumors in Children: Progress to Date

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Abstract

Anaplastic lymphoma kinase (ALK) is an oncogenic tyrosine kinase that is deregulated due to a variety of molecular mechanisms in pediatric cancer. They include chromosomal translocations, activation mutations, and gene amplifications. Since the initial discovery of ALK as an oncogenic tyrosine kinase involved in the chromosomal translocation t(2;5)(p23;q35) in 1994, more than 20 translocation partners of ALK have been identified in various cancers. Furthermore, deregulation of ALK tyrosine kinase activity is critical for the pathogenesis of several other pediatric tumors, including neuroblastomas and inflammatory myofibroblastic tumors. The recent discovery of ALK translocations in adult lung cancer patients (non-small cell lung cancer) has accelerated the development of inhibitors of ALK tyrosine kinase as therapeutic agents. While excellent clinical response has been observed in many patients, the acquisition of clinical resistance to ALK inhibition highlights the need for development of second-generation ALK kinase inhibitors and/or combination therapies that target downstream signaling mediators or antibody drug conjugates. This article provides an update on the spectrum of ALK-driven tumors in the pediatric population and the potential therapies which target these tumors.

1 Introduction

Elucidating the molecular mechanisms responsible for the development of cancer has been a driving force of cancer research for many decades. The discovery of genetic and molecular alterations associated with specific cancer types has led to more in-depth understanding of the oncogenic pathways critical for tumor formation and dissemination. Understanding the basis of cellular transformation provides a unique opportunity for potentially targeting specific pathways inherently active in the tumor and is the basis for the concept of personalized medicine. One such class of identified pathways currently being targeted by innovative therapies is constitutively activated receptor tyrosine kinases.(1, 2) The discovery of genetic alterations involving anaplastic lymphoma kinase (ALK) tyrosine kinase in anaplastic large-cell lymphoma (ALCL) and various other forms of pediatric (3) and adult cancers highlighted an opportunity to target the *ALK* oncogene. The development of specific

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inhibitors to ALK is based on the rationale that molecular targeting of the oncogene would provide an opportunity for personalized therapy and hopefully lead to improved outcomes with less toxicities. In this article, we provide an overview of the *ALK* gene and resulting protein, discuss pediatric cancers which are driven by ALK, and provide an overview of potential therapies which target ALK.

2 Anaplastic Lymphoma Kinase (ALK)

ALK is a receptor tyrosine kinase gene first identified by Morris et al.(4) in 1994 as a result of investigating a common chromosomal abnormality found in ALCL. The chromosomal rearrangement t(2;5) identified in ALCL in the 1980s led to the discovery of the nucleophosmin (*NPM*) gene at 5q35 and *ALK* gene at 2p23 as the two genes responsible for this translocation. Further research demonstrated that the *NPM-ALK* fusion gene in ALCL results in the expression of a constitutively active ALK tyrosine kinase. Like all receptor tyrosine kinases, ALK possesses an extracellular ligand binding region, a transmembrane domain, and a cytoplasmic kinase region. Physiologic ALK signaling occurs when ligand-induced homo-dimerization of the extracellular domain activates the intracellular tyrosine kinase. The activated kinase stimulates downstream signaling involving pathways thought to control cell proliferation, progression, and survival.(1, 5) Normal expression of ALK is limited to the developing nervous system, with a potential role in neuronal development.(4) In contrast to normal ALK expression, translocations involving *ALK* result in ligand-independent activation. Typically, the translocation generates a fusion protein where the partner protein to ALK supplies a domain that promotes dimerization. This allows the ALK fusion kinase to phosphorylate, creating a constitutively activated kinase. This aberrant signaling results in unregulated tyrosine kinase activity shown to be oncogenic in a number of cancers.(2, 6) While deregulated ALK activity is most commonly a result of a gene translocation involving *ALK*, mutations and gene amplifications of *ALK* have also been implicated in oncogenesis.(7, 8)

3 ALK-Positive Tumors

3.1 Anaplastic Large Cell Lymphoma

ALCL is a distinct form of non-Hodgkin lymphoma that accounts for 10–15 % of all childhood lymphomas.(9) First described in 1985 by Stein et al.,(10) ALCL is a T- or null-cell lymphoma characterized by the malignant cell expression of CD30. The vast majority of ALCL in children is ALK positive, which differs from adults where ALK-negative cases predominate. Constitutively activated ALK has been postulated to be the pathogenesis for the majority of ALCL cases. In fact, since 2008 the World Health Organization has recognized ALK-positive ALCL and ALK-negative ALCL as two separate diseases, making the distinction based on the molecular pathway that leads to oncogenesis.(11) Numerous translocations involving ALK have now been implicated in the development of ALK-positive ALCL with the most common being NPM-ALK.(3) While all translocations lead to an activated ALK fusion kinase, phenotypic and pathologic differences exist based on the partner gene to *ALK*. For example, *NPM* encodes a nucleolar domain which explains why ALK staining associated with t(2;5) occurs in the nucleus and cytoplasm while other ALCLs only express NPM in the cytoplasm. Clinically, ALK-positive ALCL occurs most frequently

in the first three decades of life and is characterized by advanced disease at presentation (75 % of pediatric ALCL) with a high incidence of nodal involvement (>90 %), frequent association with B symptoms (75 %), and frequent extra-nodal involvement including skin (25 %), lung (10 %), bone (17 %), and liver (8 %).(9, 12) Central nervous system involvement is rare.

A wide range of chemotherapy strategies have been used in children with ALCL. However, no intervention has been able to improve on the approximate failure rate of 25–30 % that exists regardless of treatment strategy.(12–17) The addition of vinblastine failed to show any improvement in survival. (14) Another study showed no advantage to intense multi-agent chemotherapy given over 11 months compared to other regimens.(12) Intensification with intermediate-dose methotrexate and high-dose cytarabine did not improve outcome.(13) Intensification with high-dose cytarabine, etoposide, and methotrexate did not improve outcome in high-risk patients. Another study used a modified acute leukemia regimen with similar results. (15) In addition, progression while receiving chemotherapy portends a very poor prognosis in children with ALCL. In one study, only 25 % of patients who relapsed on therapy survived, even with aggressive salvage therapy.(17) In summary, intensification with chemotherapy including additional agents, increased length of therapy, or increased dosing has not improved survival over standard chemotherapy. Based on these studies, there is significant interest in shifting treatment paradigms. And since pediatric ALCL is driven by aberrant ALK in the vast majority of cases, this provides an excellent potential target to increase survival in this rare disease.

3.2 Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor in children, with an annual incidence of approximately 650 cases per year in the USA. It is a cancer of very early childhood with less than 10 % of cases occurring in children over 5 years of age.(18) Clinically, neuroblastoma exhibits a wide range of phenotypes and is stratified into low-, intermediate-, and high-risk disease. While low- and intermediate-risk diseases have good prognoses, high-risk neuroblastoma is very aggressive with a high mortality rate.(18, 19) Unfortunately, high-risk neuroblastomas represent the majority of neuroblastomas. Clinical trials have focused on intensifying treatment for high-risk disease. As opposed to ALCL, intensification has improved long-term survival.(19, 20) Current treatment derived from these clinical trials includes intensive chemotherapy, surgery, radiation, hematopoietic stem cell transplantation, 13-cis-retinoic acid (isotretinoin), and biologic therapy with monoclonal antibody therapy. Despite the improvements in survival with intensification, the survival rate of high-risk disease is still only approximately 40 %.

Pathologically, neuroblastoma is a neuroendocrine tumor derived from neural crest tissue. Pathologic and molecular evaluation is essential to stratifying risk in neuroblastoma as histology, the *MYCN* oncogene amplification status, ploidy, and the presence of 1p or 11q deletions all influence risk category determination. *MYCN* amplification is the strongest prognostic factor for high-risk disease and poor outcomes.(18) Unfortunately, *MYCN* has yet to become a viable target for therapeutic intervention, necessitating the search for other potential therapeutic targets. As opposed to *MYCN*, which is common, a small percentage

(~8–10 %) of neuroblastomas express aberrant *ALK*.(7) Interestingly, hereditary neuroblastoma is characterized by activating mutations of the ALK gene within regions of the kinase domain that have been shown to be an oncogenic-driven mutation.(8) Multiple researchers have demonstrated that *ALK* mutant proteins in neuroblastoma possess a gain-of-function kinase activity sustaining downstream activation of cellular signaling pathways. The *ALK* mutations identified differ from other tumors in that they are not translocations but rather point mutations and gene amplifications. In addition, *ALK* mutations tend to occur in tumors that also possess MYCN amplification. Furthermore, a study of 491 patients with sporadically occurring neuroblastoma showed that aberrant ALK was associated with metastasis at diagnosis ($p < 0.0001$) and death ($p = 0.003$).(8) It is interesting to hypothesize that a percentage of seemingly very high-risk neuroblastomas may be driven by ALK, for which there are now potential therapeutic targets.(21)

3.3 Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumors (IMTs) are rare mesenchymal tumors. There are only an estimated 150 cases per year in the USA in all ages, with most occurring in children and young adults. Pathologically, IMTs are characterized by neoplastic spindle cells mixed with reactive inflammatory cells. In 1999, translocations involving *ALK* were identified in three cases of IMT.(22) Further studies have estimated that approximately 50 % of IMTs exhibit *ALK* translocations. The two most common translocations are TPM3-ALK and TPM4-ALK, which have also been described in ALCL.(23) Similar to ALK-positive ALCL, ALK-positive IMTs tend to occur in younger patients and have a better prognosis than ALK-negative disease. Most tumors occur in the soft tissue or viscera and have an indolent course. IMTs can be cured by surgical resection but approximately 10–15 % show a more aggressive course. These tumors do not respond to traditional chemotherapy or radiation, making therapeutic interventions targeting ALK useful in metastatic disease or unresectable tumors.(24)

3.4 Other Cancers

Although exceedingly rare in children, *ALK* translocations are seen in some forms of lung cancer. Approximately 8 % of non-small-cell lung carcinomas (NSCLC) possess a chromosomal translocation involving *ALK* that plays a role in their development. Most of these are a result of translocations such as the EML4-ALK translocation. It must be noted that other tumors including breast cancer, esophageal cancer, glioblastoma, rhabdomyosarcoma, and diffuse large B-cell lymphoma may express ALK but the role of ALK in tumorgenesis in these tumors is unclear.(6)

4 Therapeutic Agents

4.1 ALK Inhibitors

Tyrosine kinases are critical components of cellular pathways affecting cell proliferation and survival. Recent research has demonstrated that inhibitors of oncogenic kinases can produce excellent anti-tumor activity. (25) Because ALK is not widely expressed in normal tissue, ALK kinase inhibition would seem to be an ideal target for cancers that are driven by ALK.

Currently, there are several new drugs that target oncogenic ALK. Crizotinib was the first ALK inhibitor to be tested in the clinical setting against ALK-driven tumors. Crizotinib is an inhibitor of receptor tyrosine kinases including ALK and hepatocyte growth factor receptor (HGFR, c-Met).(26) In preclinical studies, crizotinib inhibited ALK phosphorylation, resulting in potent antitumor activity in ALK-positive ALCL cells but not ALK-negative cells. Crizotinib was also shown to have antitumor activity in mice with tumors that express the ALK fusion protein.(27)

Crizotinib has been evaluated in two single-arm adult clinical trials for the treatment of locally advanced or metastatic ALK-positive NSCLC.(27) The objective response rates were 50 and 61 % in these two studies, leading to US FDA approval for crizotinib for patients with locally advanced or metastatic ALK-positive NSCLC. In these studies toxicity was also manageable. Among the 397 patients for whom information on deaths and serious adverse reactions are available, the most common adverse reactions (≥25 %) were vision disorder, nausea, diarrhea, vomiting, edema, and constipation, with few grade 3–4 adverse reactions. The rates of treatment-related adverse events resulting in permanent discontinuation were 6 % in one study and 3 % in the other. Serious adverse events in ≥2 % of patients included pneumonia, dyspnea, and pulmonary embolism.

Crizotinib is also effective in treating patients with relapsed ALCL. A report in the *New England Journal of Medicine* reported two adult patients with recurrent ALK-positive ALCL who achieved complete responses after receiving single-agent crizotinib.(29) These authors updated their experience at the European Hematology Association in June 2012 reporting a total of nine patients with ALK-positive lymphoma (30). Of the nine patients, there were seven responses and four durable responses, demonstrating clear activity in ALK-positive ALCL.

A phase I/II study of crizotinib in children has enrolled 57 fully evaluable subjects, including eight with ALCL.(31) Six dose levels (100, 130, 165, 215, 280, 365 mg/m^2/dose) were evaluated in 29 patients in stratum A1. The toxicity profile for stratum A1 has been good with dose-limiting toxicities (DLTs) reached in two of seven patients at 215 mg/m^2/dose twice daily (grade 3 dizziness, grade 5 intra-tumoral hemorrhage) and one of six at 365 mg/m^2/dose twice daily (grade 4 liver enzyme elevation). A separate stratum A2 consisting of 18 patients with known *ALK* mutations were enrolled at one dose level lower than A1 stratum. One patient experienced a DLT of grade 4 neutropenia. Eight patients with ALCL have received crizotinib (six at 165 mg/m^2/dose twice daily, which is roughly equivalent to the dose used in the adult studies, and two at 280 mg/m^2/dose twice daily). Of the eight patients, there have been seven complete responses for a complete response rate of 88 %. The study is ongoing and results of responses in other tumors such as neuroblastoma and IMT are unknown.

There are other ALK inhibitors in various stages of drug development (see Table 1). AP26113 is an ALK/EGFR (epidermal growth factor receptor) inhibitor which in preclinical testing has been shown to be effective in crizotinib-resistant cell lines.(32) The drug is currently in a phase I/II study. CH5424802 (AF-802) is a selective ALK inhibitor. The phase I study in adults demonstrated that the highest dose level did not reach a maximum tolerated

dose.(33) Adverse effects were minimal and the phase II portion of the study is ongoing. LDK378 is a small-molecule inhibitor of ALK but not c-MET.(34) The phase I study demonstrated tolerability and some responses in ALK-positive lung cancer, leading to further ongoing clinical trials testing this agent. ASP3026 is a selective ALK inhibitor shown to be more potent that crizotinib in preclinical models.(35) Phase I clinical trials are ongoing. X-396 is a selective ALK inhibitor that does not inhibit c-MET.(36) Preclinical data demonstrates positive responses in cell lines, which have led to the opening of a phase I clinical trial utilizing this agent. In addition, there are other agents that have been found to inhibit ALK in preclinical testing, which may be in clinical trials at the time of publication. In summary, there are a large number of small-molecule ALK inhibitors, some of which have unique characteristics currently undergoing clinical trials.

4.2 Antibody Targeting of ALK

While there are a plethora of small-molecule inhibitors to ALK in development (and one already FDA approved), there is also a rising interest in therapeutic antibody targeting of ALK. Preclinical testing in neuroblastoma cell lines has demonstrated that the combination of ALK inhibitors with ALK antibody therapy may work synergistically by inducing ALK expression on the cell surface, thus increasing the effectiveness of antibody therapy.(37) In this way, the combination of drugs may be especially helpful in treating cancers which harbor ALK but show decreased sensitivity to ALK inhibitors.

4.3 Inhibitors of Downstream Signaling Pathways

Although the downstream signaling pathways activated by ALK have not been completely characterized, it appears, at least in ALCLs that a number of different pathways including the Janus kinase 3 (JAK3)–signal transducer and activator of transcription 3 (STAT3) pathway, the phosphoinositide 3-kinase (PI3K)-AKT pathway, and the Ras-extracellular signal-regulated kinase (RAS-ERK) pathway are activated.(3) This in turn leads to cell cycle progression, cell survival, and cell proliferation. Many of these pathways are activated in transformed cell lines and ALK inhibition leads to decreased phosphorylation of these signaling proteins. Importantly, many of these pathways are already being targeted in preclinical setting and early phase I studies.(6) For example, STAT3 inhibitors result in apoptosis of ALCL cells in xenograft mouse models and represent a tractable target. While exciting preclinically, caution must be used as different *ALK* translocations activate different signaling abnormalities and phenotypes, making it important not to make generalizations from one form of ALK-driven tumor to others. We expect these pathways to become targets for future drug development as the specific causes of oncogenesis due to activated ALK are further elucidated.

4.4 Combination Therapy

Small-molecule inhibitors have been utilized successfully as single agents and in combination with chemotherapy in some cancers. For example, imatinib has been utilized as a single agent with great success in chronic myelogenous leukemias and gastrointestinal stromal tumors as it blocks the inciting molecular change responsible for the cancer.(38) On the other hand, imatinib has been used in combination with chemotherapy in the treatment of

acute lymphoblastic leukemia associated with the BCR-ABL translocation.(39) We expect that crizotinib and future ALK inhibitors will be utilized similarly. For example, ALCL is responsive to traditional chemotherapy in ~70 % of patients. Therefore, we hypothesize that the addition of an ALK inhibitor could potentially increase survival and/or decrease the intensity of the other chemotherapy. However, in IMTs, crizotinib appears to be effective as a single agent as ALK drives the tumor and no other therapy has been shown to result in a meaningful response.

4.5 Vaccination Against ALK

ALK is an ideal target for the development of an anti-tumor vaccination strategies for therapy. There is already evidence in patients with ALCL that ALK induces immunogenicity. Not only does ALK induce an immune response but studies have shown that patients with the most robust immunologic response have improved survival.(40) A vaccine strategy could potentially increase the host response, thus complementing other therapies. Vaccines would hopefully induce long-term immunity as ALK-driven tumors appear to be dependent on ALK. While only speculative at this time, it is interesting to contemplate the potential application of anti-tumor vaccination as a preventative therapeutic option for ALK-driven tumors such as hereditary neuroblastoma.

5 Conclusion

Novel cancer therapies that target specific molecular events characteristic of the tumor are becoming increasingly important. In this sense, it is clinically relevant that alterations of *ALK* have been implicated in tumor oncogenesis across a wide variety of cancers. Cancer medications should no longer be thought of in terms of types of cancer they treat but rather the molecular pathways they target. ALK inhibitors are now following the path established by imatinib. If preclinical models and early drug testing predict the future, inhibition of the ALK oncogenic kinase will greatly benefit a number of patients across a broad range of cancers. However, there is still much to be learned. Additional pediatric trials to evaluate novel ALK inhibitors are needed as crizotinib is the only drug being tested in pediatric cancers. Defining the downstream signaling pathways of ALK, the cancer cell's dependence on ALK signaling in cancers with *ALK* alterations, the mechanisms of both primary and acquired resistance, and the optimal combination treatments would all immediately impact patients with ALK-driven tumors.

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Table 1

Potential therapeutic agents for anaplastic lymphoma kinase-driven pediatric tumors

Agents	Drug	Company	Targets	Susceptible tumors	References
ALK inhibitors	Crizotinib	Pfizer	MET/ALK	ALCL, IMT, NB	(26)
	CH5424802 (AF-802)	Chugai Pharmaceutical	ALK	ALCL, IMT, NB	(41)
	ASP3026	Astellas Pharma	ALK	ALCL, IMT, NB	
	LDK378	Novartis	ALK	ALCL, IMT, NB	
	AP26113	Ariad	ALK/EGFR	ALCL, IMT, NB	(42)
	2-Acyliminobenzimidazoles	Amgen	ALK	ALCL, IMT, NB	(43)
	X-396	Xcovery	ALK	ALCL, IMT, NB	
	GSK-1838705	GlaxoSmithKline	ALK/IGF1R	ALCL, IMT, NB	
	NMS-E628	Nerviano Medical Sciences	ALK/TRK	ALCL, IMT, NB	
Inhibitors to downstream targets	Dasatinib	Bristol Myers Squibb	SRC	ALCL	(44),(45)
	Tanespimycin	Bristol Myers Squibb	HSP90	ALCL	(46)
	GSK-2141795	GlaxoSmithKline	AKT	ALCL	(47)
	BP-1-102	NA	STAT3	ALCL	(48),(49)
Vaccination	NA	NA	NPM-ALK	ALCL	(50)

AKT protein kinase B, *ALCL* anaplastic large cell lymphoma, *ALK* anaplastic lymphoma kinase, *EGFR* epidermal growth factor receptor, *HSP90* heat shock protein 90, *IGF1R* insulin growth factor receptor 1, *IMT* inflammatory myofibroblastic tumors, *MET* N-methyl-N′-nitro-N-nitroso-guanidine (MNNG) HOS transforming gene, *NA* not available, *NB* neuroblastoma, *NPM* nucleophosmin, *SRC* sarcoma, *STAT3* signal transducer and activator 3, *TRK* tropomyosin-receptor kinases