

Current and future treatment of anaplastic lymphoma kinase-rearranged cancer

Luca Mogni

Luca Mogni, Molecular Oncology Lab, Department Health Sciences, University of Milano-Bicocca, 20900 Monza, Italy

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Correspondence to: Luca Mogni, PhD, Molecular Oncology Lab, Department Health Sciences, University of Milano-Bicocca, Via Cadore 48, 20900 Monza, Italy. luca.mogni@unimib.it
Telephone: +39-02-64488148
Fax: +39-02-64488363

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Abstract

Aberrant forms of the anaplastic lymphoma kinase (ALK) are involved in the pathogenesis of several types of cancer, including anaplastic large cell lymphoma, non-small-cell lung cancer (NSCLC), inflammatory myofibroblastic tumors, colorectal cancer, neuroblastoma

and others. In general, the ALK catalytic domain is rearranged and fused to a dimerization domain encoded by an unrelated gene. Less frequently, full-length ALK is activated by point mutations. The common theme is unregulated firing of ALK downstream signalling, leading to uncontrolled cell division and increased cell survival. ALK-driven tumors can be treated with Crizotinib, an orally available dual ALK/MET inhibitor, currently approved for advanced ALK-positive NSCLCs. Crizotinib-treated patients achieve high response rates, with an excellent toxicity profile. However, drug-resistant disease often develops, particularly in NSCLC patients. The processes leading to drug resistance include both ALK-dependent (point mutations or gene amplification), as well as ALK-independent mechanisms, which are here briefly discussed. Recently, Ceritinib has been approved for Crizotinib-refractory NSCLC, further extending patients' survival, but resistance again emerged. Novel ALK kinase inhibitors are currently under clinical development, showing great promise for improved efficacy in drug-resistance disease. It is opinion of the author that drug-resistance is likely to arise under any treatment, due to intrinsic heterogeneity and adaptability of cancer. To prevent or delay this phenomenon, we need to treat less advanced disease, with drugs that are rapidly effective in order not to allow enough time for tumor evolution, and we want to have more and more drugs with non-overlapping resistance profiles, for subsequent lines of targeted therapy. Finally, the use of drug combinations may exponentially decrease the chances of resistance.

Key words: Anaplastic lymphoma kinase tyrosine kinase receptor; Protein kinase inhibitors; Drug resistance; Crizotinib; Drug combinations

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Core tip: In this Editorial article, I discuss the issue of anaplastic lymphoma kinase (ALK) driven cancer and its specific treatment with selective ALK tyrosine kinase inhibitors. The problem of acquired drug resis-

tance is shortly reviewed and clinical data with novel investigational ALK inhibitors are presented. The possibility of specific combination therapies is briefly discussed.

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INTRODUCTION

This year marks the 55th anniversary since the first specific oncogenic alteration was described^[1]. It took over 40 years since the initial observation of the Philadelphia chromosome, to bring a concrete benefit to the patients carrying such abnormality^[2]. However, the discovery of imatinib was not simply the end of a medical problem, but it represented the beginning of a new era in cancer therapy. Personalized medicine is now a reality. Curiously, about the time when imatinib was described for the first time, a new fusion oncogene was identified in a subset of non-Hodgkin lymphoma patients and its catalytic portion was named after the disease, anaplastic lymphoma kinase (ALK)^[3]. It is astounding to think that this time it took only 12 years before a specific treatment was administered to ALK+ patients (NCT00585195; study start 2006)^[4].

ALK is a receptor tyrosine kinase whose expression is normally restricted to the developing neuronal tissue. When activated, two ALK molecules dimerize and trans-phosphorylate on specific tyrosine residues, thus triggering downstream signaling, which includes the Ras/MAPK, PI3K/AKT, Cdc42/Rac and JAK/STAT pathways^[5]. Aberrant activation of ALK kinase is oncogenic and it is found in several cancers, including anaplastic large-cell lymphoma (ALCL), non-small cell lung cancer (NSCLC), inflammatory myofibroblastic tumor, neuroblastoma, as well as thyroid, colorectal and breast cancer^[5]. In most cases, constitutive ALK activation is caused by chromosomal rearrangements that lead to expression of fusion oncoproteins comprising an amino-terminal dimerization region derived from different 5'-fusion partners (NPM1, EML4, KIF5B, and many others)^[6] and a carboxy-terminal kinase domain derived from the ALK gene. These fusion proteins are aberrantly expressed in tissues where ALK is not normally expressed, and constitutively activated by means of the dimerization domain, with no need of ligand. In neuroblastoma, full-length ALK is activated by point mutations in its kinase domain, that are thought to force the kinase fold into a permanently active conformation^[7].

The extremely low physiological expression level of ALK in normal cells, together with the demonstrated driving oncogenic role in tumor cells, make ALK fusion proteins a perfect therapeutic target.

CRIZOTINIB, FIRST-IN-CLASS ALK INHIBITOR

Preclinical data clearly supported the use of ALK inhibitors in ALK-driven malignancies^[8]. Translation of these data to the clinic led to accelerated approval of Crizotinib (PF-02341066, Xalkori™, Pfizer Inc.) an ALK/MET inhibitor launched in 2011, which is currently the front-line therapy for ALK+ NSCLC^[4,9]. In particular, phase III trials showed a significant advantage of Crizotinib vs chemotherapy in terms of progression-free survival (PFS) and response rate (RR), both in chemotherapy-pretreated and naïve patients^[10,11]. Although most trials only evaluated Crizotinib in NSCLC patients, clinical reports on its use in other tumors indicated that all ALK+ cancers may be effectively treated with ALK inhibitors^[12-14]. Notably, in contrast to short-lived responses in NSCLC (PFS is usually < 1 year), approximately half of ALCL patients who achieve a complete remission (CR) stay disease-free for prolonged periods, up to > 3 years at data cutoff^[14]. This may relate to the ability of Crizotinib to eradicate tumor-propagating ALCL cells^[15]. Importantly, Crizotinib has limited side effects, usually mild and reversible. Most common adverse events include nausea, emesis, fatigue, diarrhea and visual disturbances. Grade 3 elevations in alanine and aspartate aminotransferases were observed in a small fraction on patients. In addition, QTc prolongation was observed in 2.7% of patients across various clinical trials. Few cases of esophageal ulceration, regressed upon drug discontinuation, were also reported.

RESISTANCE TO CRIZOTINIB

Despite impressive efficacy, resistance to Crizotinib is a major hurdle, leading to treatment failure in most NSCLC patients. Several mechanisms of drug-resistance have been described. Approximately one-third of the patients develop a clone that carries point mutations in the ALK kinase domain, which render the enzyme refractory to inhibition by Crizotinib^[16,17]. In other cases, activation of bypass signaling pathways allow the cells to grow independently of ALK^[17,18]. While point mutations are generally considered to pre-exist in a very small subclone that is selected by the drug and expands under treatment, bypass signaling is thought to be an adaptive mechanism. In some patients, amplification of non-mutated fusion gene leads to resistance, simply by gene dosage^[17]. These cases may be treated by a drug increase, or, as suggested by preclinical evidence of drug-dependency in cells with oncogenic signal overflow, by a drug holiday^[19] (and our unpublished data).

Point mutations have been extensively studied both *in vitro* and *in vivo*. Similarly to most first-generation inhibitors, Crizotinib causes the selection of cells harboring a mutated gatekeeper residue^[20], in this case a Leu to Met substitution at position 1196 of ALK. The gatekeeper is a key residue that controls access to the

active site. When it is replaced by bulkier aminoacids, as is the case of the L1196M mutant of ALK, it can cause steric clash with the drug, impeding inhibitor binding. Drugs that are not affected by the aminoacid change, or more potent inhibitors that are still clinically active despite an affinity loss, are needed to overcome such mutants. In our laboratory, we observed the selection of a L1196Q mutant in NPM-ALK+ cells *in vitro*, under Crizotinib treatment^[21]. In addition to gatekeeper mutants, several other mutations have been described in patients, as well as in preclinical models^[14,17,22-24], spanning the ALK kinase domain from the region immediately aminoterminal to the α C helix, to the DFG motif. Some mutants directly affect drug binding, while others are believed to alter the kinetics or the conformational equilibrium of the kinase, causing a shift towards a more active conformation.

NEXT-GENERATION ALK INHIBITORS

Resistance to Crizotinib has fostered the search of novel, second-generation ALK inhibitors that may overcome resistant clones. Ceritinib (LDK378, Zykadia™; Novartis, Switzerland) showed great efficacy in ALK+ NSCLC patients, both Crizotinib-resistant and naïve^[25], with limited side effects, in a phase I trial, leading to fast-track approval by FDA in 2014. More trials are ongoing, but the message is that resistant patients can be effectively treated, thus further extending overall survival (OS) of these patients. Interestingly, patients that had no prior Crizotinib display a much better PFS curve compared to Crizotinib-resistant/intolerant individuals (50% vs 25% remain progression-free after 24 mo) although the data were still immature at cutoff. RRs in TKI naïve patients are similar with Crizotinib and Ceritinib, however a direct comparison between the two drugs in first-line treatment has not been done yet. Moreover, whether sequential or combined treatment will yield better outcomes is not known. The combined OS of Crizotinib-Ceritinib sequential therapy was shown to be 49.4 mo in a recent retrospective analysis of metastatic NSCLC^[26]. As a comparison, OS from metastatic diagnosis in a comparable group of ALK-wild-type controls were approximately 24 mo^[9]. Unfortunately, Ceritinib-resistant mutants do arise under treatment^[27]. In particular, substitutions at F1174 and G1202 residues have been observed in lung cancer patients progressing on Ceritinib.

Alectinib (CH5424802, Alecensa™) co-developed by Roche and Chugai, demonstrated impressive efficacy in EML4-ALK+ NSCLC patients: phase I - II studies reported 93% RR in TKI-naïve patients and 55% in patients who had progressed on Crizotinib, including brain metastases^[28,29], with mostly mild (grade 1-2) side effects. Updated results from the AF-001JP study confirmed 93.5% RR including 19.6% CRs. Follow-up indicated a 2-year PFS of 76% (median PFS not reached at median follow-up > 30 mo)^[30]. The drug is now approved for NSCLC patients in Japan. Once again,

however, resistance occurs, although at lower frequency compared with Crizotinib. Mutations at I1171, F1174 and G1202 were observed in various analyses^[31,32].

Preliminary phase I - II results with Brigatinib (AP26113, ARIAD Pharmaceuticals) were recently presented at AACR 2015^[33]. The compound showed pan-ALK inhibitory activity. An interesting analysis showed that all clinically reported ALK mutants are sensitive to Brigatinib concentrations that are well below the determined mean plasma levels, indicating that the drug may be able to overcome all mutants and possible prevent or limit resistance. Again, the G1202R mutation appears to be somewhat borderline, suggesting that this mutant might be expected to emerge under Brigatinib therapy. Indeed, preclinical work indicates that although G1202R mutant xenografts responded to Brigatinib better than to other ALK inhibitors, yet no regression was achieved. In an *in vitro* assessment of NPM-ALK and EML4-ALK mutants sensitivity to clinically relevant inhibitors, we noted that G1202R is the most intractable mutant of all^[34]. Only the new compound PF-06463922 was able to inhibit this mutant at low nanomolar doses^[35]. PF-06463922 is a very potent and selective ALK/ROS1 inhibitor undergoing phase I evaluation, with a very large therapeutic window^[36]. Indeed, recent preclinical *in vivo* data demonstrate potent PF-06463922 activity against G1202R mutant xenografts, as well as other mutations^[37].

The analysis of all clinical data available so far with second-generation ALK inhibitors highlights an interesting phenomenon: in most trials, RRs in Crizotinib-resistant patients were higher than expected based on the frequency of ALK-dependent resistance, which overall accounts for approximately 30%-40% of cases. If the numbers are correct, we have to postulate that the new drugs are able to kill ALK-independent resistance. This may occur by inhibition of bypass pathways (for example Brigatinib is a potent EGFR inhibitor; Ceritinib blocks IGF1R). If this is the case, then the reciprocal occurrence may also be true, with Crizotinib effectively blocking second-generation inhibitors-resistant tumors possibly driven by MET activation.

COMBINATION THERAPY

The problem of drug-resistance is really a major issue in cancer. Even very effective targeted therapies eventually fail, especially in highly heterogeneous diseases such as NSCLC. Knowing the cause of resistance helps in designing new and more effective drugs, which however in turn select for additional, perhaps more aggressive resistant clones. One alternative path to tackle such problem may be represented by combination therapies, since it is statistically more difficult for a cancer to acquire simultaneous resistance to more than a drug. However, combinations need to be rationally designed based on deep knowledge of the tumor biology, and thoroughly validated. For instance, combining ALK inhibition with anti-CD30 therapy (Brentuximab vedotin, Adcetris®,

INN) may have synergistic efficacy in NPM-ALK+/CD30+ ALCL. Similarly, ALK inhibitors may be combined with blockers of bypass pathways, or downstream effectors such as mTOR or PI3K inhibitors. Although attractive, these strategies have yet to be fully explored and validated in relevant models. Nevertheless, they may represent a logic way to try and eradicate the disease.

CONCLUSION

In conclusion, a new era has opened for ALK+ cancer patients. Although it is difficult to foresee definitive cure, due to the tremendous ability of advanced tumors to adapt to a new environment, we can extend life expectancy of these patients significantly, with at least the aim to make it a chronic disease. Although only few patients have been described, it seems that at least for ALK+ lymphoma this goal is not very far^[14].

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