We are witnessing an exciting era in cancer therapy. Since the appearance of the first ABL inhibitor, imatinib (Gleevec®, Glivec®; Novartis, Switzerland) in 1996 (1), a rational, targeted approach to fight cancer has been more and more widely sought. Not only therapy is changing, from general cytotoxicity to specific oncogene inhibition, but also the way tumors are classified and patients stratified is being revolutionized.

A new report on a novel targeted drug was recently published in the New England Journal of Medicine, describing the activity of a second-generation inhibitor of ALK (2). ALK was first cloned as the carboxyterminal part of a chimaeric oncogene in anaplastic large-cell lymphoma (3). Since then, mutated/rearranged versions of ALK have been recognized as driver oncogenes in several hematologic and solid neoplasias. In fact, the presence of oncogenic ALK is the only common factor among many diverse tumors from different tissue types, and it is relevant for tumor biology and therapy. For this reason, these diseases have been dubbed ‘ALKomas’. We can estimate approximately 200,000 new ALKoma cases each year worldwide. Among these, the vast majority is represented by ALK+ non-small cell lung cancers (NSCLCs). Although only a minor fraction (about 5%) of NSCLC patients harbor a translocated ALK gene, they outnumber all other ALK+ tumors in absolute numbers. These cases are mainly adenocarcinomas from non- or light-smokers, and are currently in a far better position than ALK-negative NSCLC patients, thanks to the introduction of the ALK inhibitor crizotinib (Xalkori®; Pfizer, USA). Recent data from a phase 3 trial comparing crizotinib with chemotherapy in patients with advanced or metastatic ALK+ lung cancer (4) showed a dramatic improvement of response rates (65% vs. 20%), progression-free survival (PFS) (7.7 vs. 3.0 months), as well as global quality of life (relief of symptoms and reduced toxicity).

Unfortunately, cancers possess incredible plasticity and adaptive capability. Therefore, even spectacular responses are often followed by drug-resistant relapses. This is exactly what happened to ALK+ NSCLC patients treated with...
Ceritinib, with a median duration of response around 8-10 months (4,5). Approximately one-third of relapses are due to point mutations in the kinase domain of ALK, that render the kinase refractory to inhibition (6-10). In other cases, ALK over-expression, or activation of alternative pathways, or yet unknown mechanisms are in place (8,11). The only therapeutic option for patients developing resistant disease is standard chemotherapy, unless another, more potent ALK inhibitor is available. The paper by Shaw et al. (2) reports on safety and efficacy of one such drug. Ceritinib (LDK378, ZYKADIA™; Novartis, Switzerland) is a selective low nanomolar inhibitor of ALK, that is able to block crizotinib-resistant ALK mutants in vitro and in preclinical animal models (12). The compound was designed starting from the previous lead NVP-TAE684, the very first ALK inhibitor described in literature (13), which unfortunately never made it to the clinic. Analysis of toxic metabolites of NVP-TAE684 and subsequent SAR explorations led to reversal of the piperidine ring as a crucial step towards safer derivatives (12). Finally, compound LDK378 was developed.

In their recent article, Shaw and colleagues describe the results from a phase 1 dose-escalation study of ceritinib in ALK+ patients. Notably, the study was designed to include any tumor harboring genetic alterations in ALK gene. This approach highlights the new emerging paradigm of molecular stratification of cancer patients, regardless of tumor histology. The primary objective was to determine the maximum tolerated dose (MTD). Secondary endpoints were safety, pharmacokinetics and anti-tumor activity. The dose-escalation phase was then followed by an expansion phase, in which all patients received the MTD, which was established at 750 mg daily. The most common adverse events were nausea, vomiting, diarrhea and elevated alanine or aspartate aminotransferase levels. All were reversible upon drug withdrawal. At 750 mg dose, mean C\text{max} was 800 ng/mL, which corresponds to approximately 1.4 µM, well above therapeutically active concentrations of the drug. Although plasma levels do not always faithfully represent intra-tumor drug concentrations (14), these data suggest that a large therapeutic window is available. This is confirmed by the observed clinical activity against tumors expressing mutant ALK-L1196M, despite in vitro data reported by the same authors in another article, showing that L1196M-mutant H3122-CR1 cells are about 30-fold less sensitive to ceritinib compared to parental wild-type cells (15).

Among patients receiving at least 400 mg/day, the overall response rate (ORR) was 58%. Breakdown of data between patients previously on crizotinib versus crizotinib-naïve ones showed little difference (56% vs. 62% ORR, respectively). Similar response rates have been observed in clinical trials with crizotinib (16). However, in terms of PFS the difference was more evident (prior crizotinib 6.9 vs. naïve 10.7 months). Interestingly, although median follow-up is short (6.9 months) and very few patients are at risk at >10 months, the curve of crizotinib-naïve patients seems to reach a plateau after 10 months. A comparable PFS curve was reported for crizotinib (16). Thus, the two drugs may perform similarly as first-line treatments. Overall survival (OS) at 12 months was 65% (median OS not reached) but 72% of patients were censored. Most importantly, confirmed responses were observed in 6 of 7 patients who had progressed on crizotinib and for whom genetic analysis revealed ALK mutations or amplification, confirming clinical activity on crizotinib-resistant ALK mutants.

The paper by Shaw et al. raises the question, whether patients will develop ceritinib-resistant ALK mutants. The answer comes from the paper published in Cancer Discovery (15): 5 relapsed biopsies (of 11 analyzed) from ceritinib-treated patients harbored mutations in either F1174 or G1202 position. In particular, one patient that relapsed on ceritinib carried a S1206Y substitution that responded well to ceritinib, but then developed a G1202R ceritinib-resistant mutant. The battle therefore is still ongoing: while researchers develop new weapons, cancer responds with new resistant mutants. The more ammunition we have, the more we can fight back. In this regard, another potent ALK inhibitor was recently evaluated in a phase 1-2 clinical trial by Roche (alectinib, CH542802). The authors reported an impressive 94% ORR in crizotinib-naïve patients (17). As the compound has been shown to block crizotinib-resistant mutants in preclinical models, a trial investigating alectinib in crizotinib-resistant patients is ongoing. It will be interesting to see if sequential or combined ALK inhibitors treatments are best suited to eradicate the disease.

In conclusion, while crizotinib significantly extended PFS (and OS) compared to standard chemotherapy, the addition of another line of specific TKI therapy appears to further prolong survival. Of note, on April 29, 2014, the U. S. Food and Drug Administration granted accelerated approval to ceritinib. As more ALK inhibitors are on the way to approval (18), we can expect a great improvement in life expectancy of these patients, as already seen with CML.

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References


