Deploying Ibrutinib to Lung Cancer: Another Step in the Quest Towards Drug Repurposing

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Exploiting the inherent promiscuity of drugs can enable recognition of important “off-target” effects that can be leveraged to repurpose drugs toward medical conditions not originally intended. Perhaps the classic example is the repurposing of imatinib, originally intended for breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 (BCR-ABL)-driven chronic myelogenous leukemia (CML), toward mast/stem cell growth factor receptor (KIT)-driven gastrointestinal stromal tumor (GIST) tumors (1). Compounds that have already demonstrated safety and utility in one disease can be rapidly redirected toward another disease entity, thereby quickening the pace of clinical trial development and proof of benefit from compounds. It is under this context that the report by Gao and colleagues (2) is important. This group took advantage of the recent US Food and Drug Administration (FDA) approval of ibrutinib, a small molecule tyrosine kinase inhibitor with activity against the Bruton tyrosine kinase (BTK) in mantle cell lymphoma (3).

Previous studies had demonstrated that other tyrosine kinases, including epidermal growth factor receptor (EGFR), were inhibited by ibrutinib (4). In their study, Gao et al. screened 39 non–small cell lung cancer cell lines for effects of ibrutinib on cell viability and observed three cell lines, all with strong EGFR signaling, which were statistically significantly affected by ibrutinib (2). This prompted follow-up experiments that demonstrated activity in additional EGFR-driven lung cancer cell lines, including the H1975 cell line, which is driven by somatically mutated EGFR along with a T790M gatekeeper mutation. This latter cell line is a good model system for the frequent T790M mechanism of reversible EGFR tyrosine kinase inhibitor (TKI) resistance, and thus the observation that ibrutinib had activity in this line was noteworthy (5,6). Further studies indicated that ibrutinib did in fact inhibit EGFR phosphorylation and signaling and had activity in vivo when employed in the H1975 mouse xenograft model. Collectively, results from Gao et al. (2) indicated a novel new potential use for ibrutinib against EGFR–driven lung cancer and suggested that ibrutinib could be utilized to overcome acquired resistance to reversible EGFR TKI through the frequent gatekeeper mutation (7).

How relevant and important is this observation in 2014, and what should one expect with deploying ibrutinib against EGFR-mutant lung cancer, based on the studies reported here, as well as other preclinical and clinical observations? First, ibrutinib can be added to the list of TKIs with some degree of activity against EGFR-driven cancers, including midostaurin, which recently was shown to have activity against T790M EGFR (8,9). One of the observations made by Gao et al. (2) was similar killing of H1975 cells with ibrutinib and afatinib, the latter being an irreversible EGFR TKI. Afatinib, as well as other irreversible EGFR TKIs such as neratinib, have been studied in both preclinical models and clinical trials, with afatinib having more data, including FDA approval for use in EGFR-mutant lung cancer (10,11). However, a sobering result of studies with afatinib and neratinib, suggested by preclinical data and validated to some extent in clinical trials, is the relative modest efficacy in patients with acquired resistance to reversible EGFR TKIs such as erlotinib and gefitinib (12,13). In the LUX-Lung 1 trial, which tested afatinib in patients with acquired resistance to reversible EGFR TKI, partial response rate was 7%, and median progression-free survival was extended from 1.1 to 3.3 months without any observed benefit in overall survival (14). No patients were reported to respond to neratinib with T790M (13). This raises concerns that ibrutinib, if behaving similarly to afatinib and other irreversible EGFR TKIs, may have limited clinical activity.

The uncertainty over potential ibrutinib use in EGFR-mutant but gefitinib/erlotinib-refractory disease is further complicated by exciting recent reports of selective mutant EGFR TKIs with activity against EGFR proteins with T790M. AZD9291 and CO-1686 are small molecules with activity in preclinical models of T790M-mediated resistance (15,16). Importantly, recent reports from ASCO 2014 have suggested impressive activity and good safety profiles in patients with acquired resistance to reversible EGFR TKIs, including patients with known T790M mutations (17,18). In addition, as Gao and colleagues point out in their discussion (2), skin rash is relatively uncommon in EGFR TKI-resistant patients; therefore, clinical observations may need to come through round-about mechanisms. Previously, “off target” effects have been realized after patients receiving therapy for one cancer have a second coexisting cancer that also responds (19). For example, Pitini et al. reported activity of dasatinib against both the primary disease, CML, as well as a coexisting squamous cell lung cancer with a driver DDR2 mutation (20). The community should stay on alert for such possibilities, and it will be interesting to see whether anything is reported for patients with both lung cancer and mantle cell lymphoma receiving ibrutinib.
Perhaps the most important aspect of this work is the recurrent story of how compounds already active in one disease can be repositioned safely and effectively toward other medical uses. This begs the question of how to ensure that these types of studies continue, as well as how to exploit the inherent promiscuity of drugs in a systemic way to guide repurposing. One way is through use of compound screening against large panels of cancer cell lines with well-characterized genetics and other underlying biology (21,22). This can uncover potential off-target drugs, similar to that observed in the screen by Gao et al. (2). A second approach would be to more systematically define and characterize off-target compounds using modern chemical biology techniques and tools. For instance, a large-scale screening approach can also be applied to less thoroughly characterized cell lines or tumor models. For these models, however, it would be necessary to compare a panel of compounds with the same intended or cognate target, which would allow for distinguishing between on- and off-target effects of individual compounds. In addition, it would be subsequently necessary to perform an unbiased and global target survey to identify the “culprit” off-target. There are many technologies, such as chemical proteomics (23), yeast three hybrid (24), and microarray-based analyses (25), that are suited for this task (26). Unfortunately, all of these require substantial financial and experimental effort and have their individual pitfalls and caveats, which collectively deter most investigators from pursuing off-target effects in a systematic fashion. However, by elucidating such off-target mechanisms in cancer cells, one would simultaneously gain critical insight into the underlying wiring of cell type–specific oncogenic signaling networks and potentially new Achilles heels within these. For instance, dissecting complex off-target mechanisms of dasatinib in lung cancer has led to novel drug combination approaches with EGFR TKI, which have been translated into clinical trials and shown the potential of dasatinib to be repurposed against DDR2-mutant squamous cell lung cancer (27,28). In another study, querying a small panel of clinical kinase inhibitors for synergistic drug combinations in BCR-ABL T315I CML cells, combined with a subsequent systems pharmacology approach to understand the underlying molecular mechanisms, led to the surprising finding that two of the most unselective compounds in the panel exhibited potent synergy, which was not just specific for this mutant background but also the product of off-target inhibition of both of these within the MAPK signaling pathway (29).

In conclusion, this area of research constitutes a tremendous untapped potential for identifying novel therapeutic approaches with drugs or drug candidates that are already known to be safe in humans. Therefore, it is desirable to see further studies, such as the present one by Gao and colleagues (2), that specifically attempt to utilize the hidden potential of clinical agents for new purposes.

References


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