SYSTEMS BIOLOGY

**Major finding:** Pretreatment with EGFR inhibitors sensitizes triple-negative breast cancers to cytotoxic agents.

**Concept:** EGFR inhibitors rewire an EGFR-driven signaling network to derepress apoptotic pathways.

**Impact:** Time-staggered treatment protocols may be generalizable to other oncogene-addicted cancers.

**TARGETED THERAPIES ARE MORE EFFECTIVE WHEN USED PRIOR TO CHEMOTHERAPY**

Unlike other breast cancer subtypes over-expressing the estrogen or progesterone receptors or harboring a HER2 amplification, triple-negative breast cancers (TNBC) do not respond to conventional hormonal or targeted treatment regimens and consequently have a worse overall prognosis. Lee and colleagues reasoned that new treatment strategies might be identified by systematic analysis of the effects of various doses and schedules of cytotoxic and targeted therapy combinations on the viability and proliferation of TNBC cells. Surprisingly, administration of the epidermal growth factor receptor (EGFR) inhibitor erlotinib several hours prior to the cytotoxic agent doxorubicin enhanced the doxorubicin sensitivity of 9 out of 10 TNBC cell lines and reduced the size of TNBC xenograft tumors. This effect was not observed when doxorubicin was added before or at the same time as erlotinib or in other breast cancer subtypes. In TNBC cells, continuous erlotinib treatment led to progressive, widespread changes in gene expression and signaling proteins, with mathematical models indicating that EGFR inhibition leads to rewiring of an EGFR-mediated network that culminates in activation of apoptotic responses. Importantly, this time-dependent response was also observed in TNBC cells with combinations of other EGFR inhibitors and cytotoxic drugs as well as in other cancer cell types with high levels of EGFR activity. Furthermore, the doxorubicin sensitivity of breast cancer cells known to be addicted to HER2 could also be enhanced by pretreatment with the dual HER2–EGFR inhibitor lapatinib. Collectively, these results identify a potential treatment regimen for TNBC and raise the exciting possibility that the time-staggered use of targeted therapies to sensitize cancers to subsequent chemotherapy may be a generalizable therapeutic strategy that will improve clinical outcome.


**Sarcoma**

**Major finding:** Regorafenib shows activity in patients with TKI-refractory metastatic GIST.

**Approach:** A phase II trial evaluated the safety and efficacy of the multi-kinase inhibitor regorafenib.

**Impact:** Regorafenib may be a third-line treatment for patients with advanced GIST.

**REGORAFENIB IS EFFECTIVE AGAINST IMATINIB- AND SUNITINIB-RESISTANT GIST**

Gastrointestinal stromal tumor (GIST), the most common form of sarcoma, is caused by activating mutations in either of the receptor tyrosine kinase genes KIT or PDGFRα. Treatment with the targeted first- and second-line tyrosine kinase inhibitors (TKI) imatinib and sunitinib, respectively, has dramatically improved the prognosis of patients with GIST. However, TKI resistance, which is usually mediated by secondary KIT mutations, eventually develops in advanced disease, and no third-line agents currently exist for the treatment of TKI-refractory metastatic GIST. Given the limited treatment options for advanced GIST, George and colleagues investigated the efficacy and safety of regorafenib, an oral multikinase inhibitor with activity against KIT, PDGFR, and multiple other targets, in 33 patients with metastatic GIST after failure of both imatinib and sunitinib. In this multicenter phase II trial, 75% of the patients achieved a clinical response, which included 4 partial responses and 22 instances of stable disease, with a median progression-free survival of 10 months. Importantly, analysis of patient biopsies from tumors that harbored KIT resistance mutations showed decreased levels of KIT activation and other downstream targets during treatment with regorafenib, suggesting that regorafenib is active against secondary KIT mutations. Although it remains unclear whether the clinical activity of regorafenib is solely due to inhibition of KIT, a compensatory signaling pathway, or both, these findings suggest that regorafenib may represent an effective third-line agent in patients with TKI-resistant GIST. A phase III trial further evaluating the efficacy of regorafenib is currently in progress.

Targeted Therapies Are More Effective When Used Prior to Chemotherapy


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