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## Clinical Trials

**Major finding:** Pazopanib controls disease in over half of patients with relapsed or refractory urothelial cancer.

**Clinical relevance:** High circulating levels of interleukin-8 were associated with shorter overall survival.

**Impact:** Pazopanib warrants further study in randomized clinical trials, perhaps in a more selected population.

### PAZOPANIB HAS SINGLE-AGENT ACTIVITY IN ADVANCED UROTHELIAL CANCER

First-line platinum-based chemotherapy is moderately effective in urothelial cancers, but most patients ultimately experience disease progression and have minimal responses to second-line single-agent or combination chemotherapy. New treatment modalities for relapsed and refractory urothelial cancers are therefore needed, and due to the highly vascular nature of urothelial cancers, targeted antiangiogenic agents are of particular interest. Necchi and colleagues conducted an open-label, single-group phase II trial of pazopanib, a multitarget kinase inhibitor with antiangiogenic activity, in 41 patients with urothelial cancer, approximately half of whom were heavily pretreated and classified as cisplatin refractory. The primary endpoint was a confirmed objective response (including partial and complete responses), and secondary endpoints included safety, progression-free survival (PFS), overall survival (OS), disease control (objective response plus stable disease), and circulating levels of angiogenic factors. Partial responses were confirmed in 7 patients, 4 of whom had aggressive upper urinary tract tumors. An additional 14 patients had stable disease, meaning that 21 patients treated with pazopanib achieved disease control. The median PFS was 2.6 months, the median OS was 4.7 months, and after more than a year, 6 patients were still alive and 4 were progression free. High baseline and posttreatment circulating levels of interleukin (IL)-8, a known contributor to the compensatory mechanism of resistance to the antiangiogenic agent sunitinib, were significantly associated with shorter overall survival, suggesting that IL-8 levels may be used to identify patients likely to benefit from pazopanib treatment. Pazopanib was generally well tolerated, although changes in bulky tumor masses induced fistulizations in 6 patients, 1 of whom died. Although patients presenting with bulky disease may be at increased risk for adverse effects, these findings provide support for further clinical evaluation of pazopanib in advanced, refractory urothelial cancer. ■

*Necchi A, Mariani L, Zaffaroni N, Schwartz LH, Giannatempo P, Crippa F, et al. Pazopanib in advanced and platinum-resistant urothelial cancer: an open-label, single group, phase 2 trial. Lancet Oncol 2012;13:810–6.*

## Cell Death

**Major finding:** Cardiac glycosides stimulate immunogenic cell death that protects against tumor growth.

**Approach:** Automated fluorescence microscopy was used to screen for drugs that induce ICD.

**Impact:** Treatment with digoxin may augment the cytotoxic effect of chemotherapeutics.

### CARDIAC GLYCOSIDES MEDIATE AN ANTITUMOR IMMUNE RESPONSE

Cell death triggered by certain chemotherapeutic drugs, such as anthracyclines, elicits an immune response that is required for efficient cytotoxicity. This immunogenic cell death (ICD) can activate anticancer immune pathways and is characterized by exposure of calreticulin at the cell surface, secretion of ATP from dying cells, and release of the high mobility group box 1 (HMGB1) protein from the nucleus. To identify additional agents that induce ICD, Menger and colleagues devised a fluorescence microscopy–based platform to detect the presence of these biochemical properties of ICD in tumor cells treated with a library of chemical agents. Anthracyclines were among the most effective compounds in promoting the hallmarks of ICD, thus validating this approach. Intriguingly, this screen also identified cardiac glycosides (CG), including digoxin (DIG) and digitoxin, as potent mediators of ICD in several human cancer cell lines. CG-mediated inhibition of the plasma membrane $Na^+/K^+$-ATPase and stimulation of $Ca^{2+}$ influx were necessary for this induction of ICD. In addition, the ability of DIG to stimulate ICD was only observed in immunocompetent mice, supporting an essential role for the immune system in facilitating the antitumor effect of CGs. Treatment with DIG augmented the ability of dying cancer cells to activate an immune response and to protect mice against subsequent tumor growth, suggesting that CGs may improve the clinical response to chemotherapeutic drugs. In support of this idea, a retrospective analysis of a matched patient cohort revealed that patients who received DIG during treatment with nonimmunogenic antitumor therapies showed a significant increase in overall survival. Although additional clinical studies are required, these results suggest that CGs may enhance the efficacy of cytotoxic anticancer drugs. ■

*Menger L, Vacchelli E, Adjemian S, Martins I, Ma Y, Shen S, et al. Cardiac glycosides exert anticancer effects by inducing immunogenic cell death. Sci Transl Med 2012;4:143ra99.*

**Note:** *Research Watch* is written by *Cancer Discovery* Science Writers. Readers are encouraged to consult the original articles for full details. For more Research Watch, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.

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CANCER DISCOVERY

# Cardiac Glycosides Mediate an Antitumor Immune Response

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