Enhanced anti-tumor efficacy by sequential application of Wnt pathway antagonists in combination with taxanes

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ABSTRACT

The Wnt/beta-catenin pathway, which signals through the frizzled (FZD) receptor family and several co-receptors, has long been implicated in cancer. We have previously demonstrated that inhibition of Wnt/beta-catenin signaling by vandetanib (anti-Fzd, OMP-1865) or ipafricept (FZD8-Fc, OMP-54F28) inhibits tumor growth, decreases tumorigenicity and induces differentiation in solid tumors. The anti-tumor effect of our Wnt antagonists is most evident in combination with chemotherapeutic agents. We sought to determine if the anti-tumor effect of Wnt pathway inhibitors varies with different chemotherapeutic agents. We compared the growth inhibitory effect of vandetanib and ipafricept with either taxanes (paclitaxel and nab-paclitaxel) or with DNA synthesis inhibitors (gemcitabine and cisplatin) in patient-derived xenograft models. Our results demonstrate that combining vandetanib or ipafricept with nab-paclitaxel compared to the combination with gemcitabine or cisplatin in pancreatic ductal carcinoma and serous ovarian cancer xenograft models. Histologic analysis in a pancreatic ductal carcinoma indicated that nab-paclitaxel increased mitotic cells and beta-catenin levels. Importantly, the addition of vandetanib to nab-paclitaxel reversed the nab-paclitaxel-induced increase in mitotic cells and beta-catenin expression. A potential mechanism to account for these results involves the observation that Wnt/beta-catenin signaling is under cell cycle control and peaks at the G2/M phase. Taxanes inhibit microtubule function and block the cell cycle at G2/M. In contrast, other chemotherapeutic agents, such as platinum compounds and nucleoside analogs, inhibit DNA synthesis and block cell proliferation at S phase. Our findings suggest that combination of Wnt blockade with chemotherapeutic agents, such as taxanes, that induce G2/M arrest may result in enhanced anti-tumor activity. The optimal synergy of anti-Wnt plus taxane combination occurs when the antibody was applied prior to taxane. Further analyses in various ovarian tumor models revealed that pre-treatment with ipafricept resulted in dysregulated beta-catenin localization within giant multi-nucleated cells and up-regulation of genes associated with Wnt/beta-catenin signaling. These results provide evidence for the enhanced anti-tumor effect of Wnt pathway inhibitors in combination with taxanes and highlights the importance of preclinical examination to identify the most efficacious combination therapy regimens and the timing of antibody action for Wnt antagonists in combination with taxanes for optimal treatment efficacy.

BACKGROUND

The Wnt/beta-catenin signaling pathway, which signals through the frizzled (FZD) receptor family and several co-receptors, plays an important role in controlling cell fate, self-renewal and maintenance of cancer stem cells. Dysregulation of this pathway has been implicated in cancer.

- We have developed two novel Wnt pathway antagonistic antibodies: Vandetanib (OMP-1865), which blocks Wnt binding and canonical signaling, and ipafricept (FZD8-Fc), consisting of a portion of the FZD8 receptor containing the extracellular ligand binding domain and a human IgG1 Fc fragment. This fusion protein blocks Wnt signaling induced by multiple Wnt family members by binding and sequestering Wnt.

- Preclinical studies show that vandetanib and ipafricept inhibit tumor growth, decrease tumorigenicity and induce differentiation in multiple patient-derived xenograft models. The anti-tumor effect of these antibodies is more evident in combination with chemotherapeutic agents.

- Recent work has demonstrated that Wnt/beta-catenin signaling is under cell cycle control and peaks at G2/M phase (Tripodi and Cell 20:453-63, 2010). Taxanes, which block cell cycle at G2/M and other DNA synthesis inhibitors are commonly used as standard-of-care chemotherapeutic agents in cancer treatment.


- We found that anti-WNT antibodies in combination with gemcitabine/nab-paclitaxel produced much greater anti-tumor effect than with gemcitabine in patient-derived pancreatic tumor models. The goal of this study is to examine whether different chemotherapeutic agents influence the anti-tumor effect of Wnt pathway inhibitors in patient-derived xenograft tumor models.

- Taxanes are more effective class of chemotherapeutic agents in combination with anti-WNT than non-taxane agents.

- The enhanced combination effect is both taxane-specific and dose-dependent. Anti-WNT plus taxane combination can be further improved by applying antibody prior to taxane.

- Intermittent sequential application of anti-WNT antagonists plus Taxane Combination Occurs When the Antibody is Applied 2-3 Days Prior to Taxane.

MATERIALS AND METHODS

Patient-derived xenograft tumors were obtained from University, Molecular Response or NDRR. Both tumors were generated at OncoMed Pharmaceuticals, Inc. Tumors were passaged subcutaneously in nude mice in up to 4 passages.

- For efficacy studies, treatments were initiated when tumors reached 100 mm². Both antibodies and chemotherapeutics were administered intraperitoneally.

- Histologic analysis used formalin-fixed, paraffin-embedded section or frozen sections. Sections were stained using Imagescope (ScanScope AT. Aperio).

- For gene analysis, RNA was isolated from tumor tissues followed by cDNA synthesis. The resulting c-DNA was analyzed by real-time PCR.

- Data are expressed as mean±S.E.M. Differences of p<0.05 are considered significantly different.