Enhanced anti-tumor effect 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 vantictumab (anti-FZD) or OMP-54F28 (FZD8-Fc) inhibits tumor growth, decreases tumorigenicity and induces differentiation in solid tumors. The anti-tumor effect of our Wnt antagonist is most evident in combination with chemotherapeutic agents. We sought to determine if the anti-tumor effect of Wnt pathway inhibitors varied with different chemotherapeutic agents. We compared the growth inhibitory effect of vantictumab and OMP-54F28 with either taxanes (paclitaxel and nab-paclitaxel) or with DNA synthesis inhibitors (gemcitabine and carboplatin) in patient-derived tumor xenografts. In a model for pancreatic ductal carcinoma, vantictumab with nab-paclitaxel was more efficacious than vantictumab with gemcitabine in inhibiting tumor growth and Wnt target gene expression (at doses of nab-paclitaxel and gemcitabine that were equivalent in their single-agent growth inhibitory effects). Histologic analysis indicated that nab-paclitaxel increased mitotic cells and beta-catenin levels. Importantly, the addition of vantictumab to nab-paclitaxel reversed the nab-paclitaxel-induced increase in mitotic cells and beta-catenin expression. An independent experiment in a severe ovarian cancer xenograft model also showed enhanced anti-tumor activity when combining OMP-54F28 with either paclitaxel or nab-paclitaxel compared to the combination with carboplatin. 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. We hypothesize that combination of Wnt blockade with chemotherapeutic agents, such as taxanes, that induce G2/M arrest may result in optimal anti-tumor activity.

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.

• The pancreatic tumors OMP-PN13 and OMP-OV19 ovari·ans were obtained from University and NDRI, respectively. Both tumors were generated at OncoMed Pharmaceuticals, Inc. Tumors were passaged subcutaneously in NOD-SCID mice up to 4 passages.

• 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.

MATERIALS and METHODS

• The pancreatic tumors OMP-PN13 and OMP-OV19 ovari·ans were obtained from University and NDRI, respectively. Both tumors were generated at OncoMed Pharmaceuticals, Inc. Tumors were passaged subcutaneously in NOD-SCID mice up to 4 passages.

• For efficiency data, treatments were initiated when tumors reached 100 mm3. OMP-PN13 tumor-bearing animals were treated with gemcitabine (25 mg/kg weekly) or nab-paclitaxel (30 mg/kg weekly) with or without Vantictumab (25 mg/kg every other week). OMP-OV19 tumor-bearing animals were treated with carboplatin (30 mg/kg weekly) or paclitaxel (10 mg/kg weekly) with or without OMP-54F28 (25 mg/kg every other week). Both antibodies and chemotherapeutic agents were administered intraperitoneally.

• Histologic analysis used formalin-fixed, paraffin-embedded section or frozen sections. Slides were scanned 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 means±SEM. Differences of p≤0.05 are considered significantly different.

CONCLUSIONS

• The anti-tumor efficacy of anti-WNT pathway inhibitors vantictumab and OMP-54F28 is enhanced in combination with taxanes relative to the combination activity with DNA synthesis inhibitors gemcitabine or platinum compounds.

• Immuno-Histologic and immuno-fluorescence analysis in OMP-PN13 pancreatic xenograft tumors indicated that nab-paclitaxel increases mitotic cells and beta-catenin accumulation. On the other hand, gemcitabine, an agent that blocks DNA synthesis at S phase, decreases mitotic cells and increases membrane-associated beta-catenin. The addition of vantictumab to nab-paclitaxel reduces the nab-paclitaxel-induced increase in mitotic cells and beta-catenin accumulation.