Student Research Conference

Taxotere as a Treatment for Ovarian Epithelial Carcinoma

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An Introduction to Ovarian Epithelial Carcinoma and Taxotere

Epithelial ovarian cancer accounts for 90% of ovarian cancers, is the most lethal gynecological cancer, and the fifth-most common cause of cancer-related deaths in women in the United States[6]. In 2016, there were an esitmated 22,280 new cases in the U.S. and the overall survival rate at 5 years is 46.2%[3]. About 10% of cases are heriditary [4]. Clinical trials have shown that the efficacy of more traditional platinum-based drugs are increased when combined with a taxane-based drug. Docetaxel, commercially Taxotere, is a taxane that has been in use since the mid-1990s and is used to treat many forms of cancer including ovarian but also; breast, lung, head and neck, gastric and prostrate carcinomas. Taxotere is derived from the needles of the European Yew tree (*Taxus baccata*) by a semisynthetic process[1] and like other taxane-based drugs, binds to microtubules during mitosis leading to apoptosis and cell death[2]. Figure 1 (top) shows the difference between untreated cancer cells (left) and cells that have been treated with taxane-based drugs (right). Many human genes have been found to be correlated with ovarian cancer with 20 to 25% of patients having hereditary linkage; a list of these genes [4] and their unmutated functions are shown in Table 1.

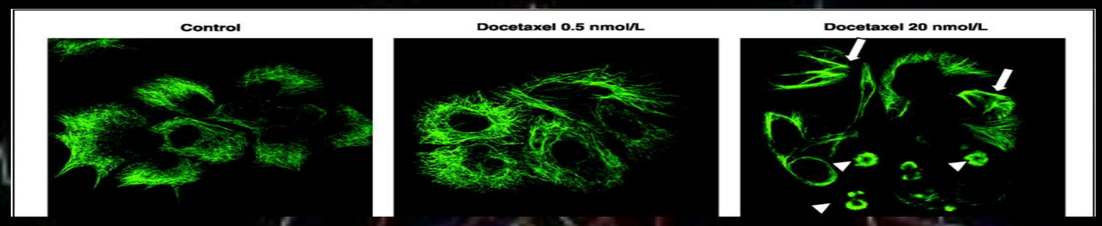

Figure 1: Microtubule inhibition via Docetaxel treatment. Arrows; microtubule bundle formation, arrowheads; aberrant mitotic cells[12]

Taxotere

As a chemotherapeutic agent, Taxotere is a semi-synthetic multi-ring structure that is delivered to the patient intravenously. Taxotere binds to the beta-tubulin subunit causing the structure to become more rigid and prevents depolymerization of the microtubules during mitosis between metaphase and anaphase.

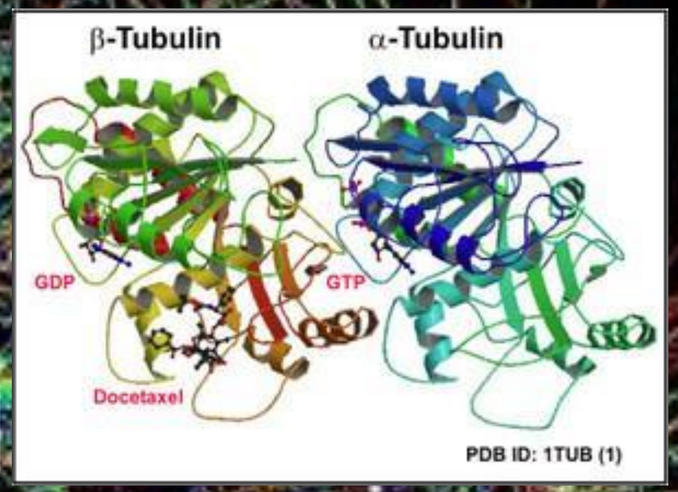

Figure 2: Taxotere also commonly known as Docetaxel interacting with the beta-tubulin subunit.

Modes of Action

Microtubules are fibrous structures composed of polymers of alpha and beta tubulin and other associated proteins. They are essential to several cellular processes including transport, signaling, and mitosis. During normal cell mitosis, microtubules are necessary for the separation of chromosomes into the two daughter cells. Taxotere stabilizes microtubules by binding to beta tubulin and inhibiting microtubule disassembly, arresting the cell in metaphase and leading to apoptosis and cell death[2]. Taxotere has been shown to be significantly more cytotoxic than other taxane-based drugs (Paclitaxel) and non-taxane based drugs (Cisplatin and Etoposide) while being less neurotoxic. For treatment of epithelial ovarian cancer, Taxotere is commonly given in conjunction with platinum-based chemotherapy drugs such as Cisplatin and Carboplatin for a synergistic effect[1].

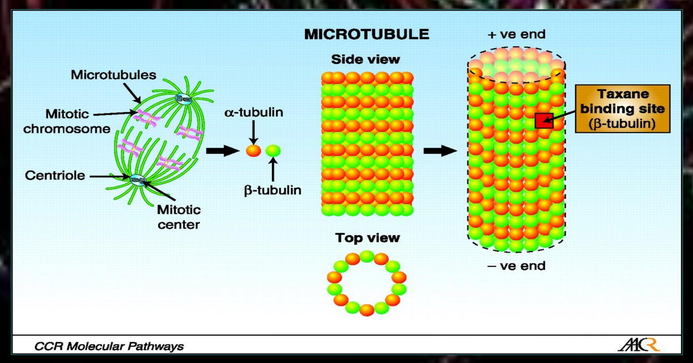

Figure 3: Microtubules are made up of alpha-tubulin and beta-tubulin which are arranged into long cylindrical chains. Microtubules have many functions such as transport, movement, signaling, and mitosis. Taxotere binds to the beta-tublin and inhibits disassembly[2].

Gene	Chromosome	Gene Function
BRCA1	17	DNA repair associated
BRCA2	13	DNA repair associated
TP53	17	Tumor protein
CHEK2	22	Checkpoint Kinase
RAD51	15	Recombinase
RAD51 Paralog C	17	Recombinase
RAD51 Paralog B	14	Recombinase
RAS51 Paralog D	17	Recombinase
BRIP1	17	BRCA1 interacting protein C-terminal helicase
PALB2	16	Partner and localizer of BRCA2
MLH1*	3	MutL homolog**
MSH2*	2	MutS homolog**
MSH6*	2	MutS homolog**
PMS2*	7	PMS1 homolog, mismatch repair system component
PMS1*	2	Mismatch repair system component
MLH3*	14	MutL homolog**

Table 1: Genes correlated with Epithelial ovarian carcinoma *MMR genes correlated with Lynch Syndrome, an inherited disorder that confers propensity to develop many types of cancer including Ovarian. **MutS and MutL proteins assist in nucleotide mismatch repair.[9]

Phase II Study of Alternative Epithelial Ovarian Cancer Treatment

Sacituzumab govitecan, IMMU-132, is an antibody drug conjugate containing the antibody hRS7 and an active metabolite of SN-38.[11] The antibody selectively binds to TROP2, an epithelial glycoprotein transmembrane calcium signal transducer overexpressed by many epithelial carcinomas. Once bound to TROP-2 the SN-38 stabilizes the topoisomerase I DNA covalent complexes. This results in breaks in the DNA, inhibiting replication and signaling apoptosis; cell death[7]. IMMU-132 is currently in Phase 2 evaluation for safety and ability as a lone chemotherapeutic agent.[10] Figure 4 (below) is a graphic of the interaction between IMMU-132 and an epithelial tumor.

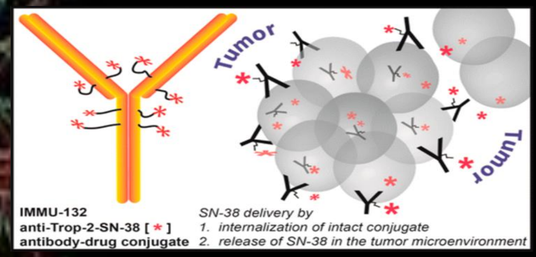

Figure 4: IMMU-132 interaction with epitheial carcinoma cells.[8]

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