

TAXANES : DELIVERY ISSUES AND RELATED COMPOUNDS

Delivery Issues

Because it is insoluble in water, paclitaxel was, until recently, available only in a Cremophor base. Cremophor, a product of the BASF Corporation, is a form of castor oil that has been treated with [ethylene oxide](#), a precursor to both [mustard gas](#) and ethylene glycol (a chemical commonly used in antifreeze and for medical sterilization). From its earliest use, the Cremophor base has been known to cause allergic reactions ([Goodman and Walsh 2001, p. 116](#)). While these are generally manageable through steroid pre-treatment, there is growing evidence that fatal allergic reactions are more common than previously suspected even among pre-treated patients, with as many as twenty percent of fatalities involving pre-treated patients ([Irizarry et al. 2009](#)).

The toxicity of the Cremophor base and the dose-limiting neuropathy have fueled a search for safer taxanes, and there are several candidates in varying stages of the drug development pipeline. For example:

Abraxane

An albumin-bound nanoparticle form of paclitaxel that eliminates the Cremophor base. It is currently [FDA](#) approved for breast cancer that has failed to respond to standard therapies or that has relapsed shortly after standard treatment, and is available to other patients through clinical trials.

Taxoprexin

A DHA-paclitaxel. Paclitaxel is bound to DHA, a naturally occurring omega-3 fatty acid. DHA-paclitaxel appears to be taken up in greater concentrations by cancer cells. More importantly, early studies indicate that it is not converted into its active form until it is metabolized within a cell. As a result, it may be significantly less toxic to healthy cells, have a longer half-life within tissues, and be capable of being administered in higher doses. Preliminary reports suggest that it has anti-cancer effects comparable to standard paclitaxel ([Homsy et al. 2008](#); [Bradley et al. 2001](#)).

Xyotax

A PG-paclitaxel. Paclitaxel is bound to poly-(L)-glutamic acid, rendering it water soluble so that a Cremophor base is unnecessary. It is also preferentially accumulated by [cancer](#) cells. Early trials indicate that PG-paclitaxel has limited toxicity until metabolized within a cell. So, like DHA-paclitaxel, it may be less toxic to healthy tissue, allowing the administration of higher doses, sustaining higher doses of the drug in the blood stream, and potentially offering greater anti-cancer effectiveness ([Singer et al. 2003](#)). However, a related compound seemed to trigger more frequent drug sensitivity reactions, possibly leading to waning clinical trials of the compound in favor of other novel taxanes

Related Compounds

Epothilones

Initially discovered in the myxobacterium *Sorangium cellulosum*, epothilones are under evaluation as taxane alternatives. The epothilones have a similar but not identical mechanism of action to the taxanes - they are microtubule de-polymerization inhibitors - but remain effective against a variety of paclitaxel-resistant cancers and appear to have lower toxicity (E.g., [Goodin et al. 2004](#)). Epothilones are delivered in Cremophor and non-Cremophor vehicles and may cause significant [neuropathy](#) (Pronzato 2008). Epothilones have demonstrated effectiveness against ovarian, prostate, breast, colon, stomach, and kidney [cancers](#) (Goodin 2008). Ironically, the development of the epothilones, first isolated in the early 1980s, was delayed nearly as long as that of paclitaxel, in part because compounds derived from nature require a longer time to identify, to understand in terms of mechanism, and to develop the complex production processes required to go from natural compound to effective quantities of drug. The development of epothilones languished partly because of industry fascination with targeted biologics like herceptin (biologics[1] are a class of cancer treatment that uses the patient's own immune system to fight cancer), and partly because the legal windows for securing necessary property rights are not well-aligned with the lengthy research needed to develop therapeutic agents from natural compounds ([Mulzer et al. 2009](#)).

Larotaxel

A semi-synthetic compound derived from the needles of yew trees, larotaxel is closer to docetaxel than paclitaxel. It acts by stabilizing microtubules, leading to cell death through apoptosis. In early clinical trials it has shown activity against paclitaxel-resistant and non-resistant cancers, and the ability to cross the blood-brain barrier, making it a potential therapy for brain metastases ([Morris and Fornier 2009](#)). Larotaxel is being

evaluated for effectiveness against non-small cell lung cancer, and breast, pancreatic, and bladder cancers.

Footnote:

1. **Biologics or biological therapy:** Also called biotherapy, immunotherapy, or biological response modifier therapy, biologics are a class of cancer treatment that uses the patient's own immune system to fight cancer. Biological therapies boost or manipulate the immune system into fighting cancer in several ways: (1) by tagging cancer cells with proteins called antibodies, which identify the cancer cells as invaders to be destroyed by the immune system; (2) by boosting the effectiveness of the immune system's killer cells, (3) by stopping or slowing the process by which abnormal cells become cancer cells, or (4) by enhancing cellular repair mechanisms that prevent damaged cells from becoming abnormal or cancerous. Because biologic therapy is more targeted, the side effects are often less severe than those caused by traditional, broadly toxic chemotherapies.

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