Supplemental: Drug Properties

**Paclitaxel** (Taxol) is highly lipophilic and requires Cremophor®EL ([CrEL, polyoxyethylated castor oil]) to be rendered available as a solution for clinical administration. Each 6 mg of Taxol (Bristol-Myers Squibb) has 527 mg of this purified CrEL and 49.7% v/v dehydrated alcohol, USP. The pharmacokinetic parameters are non-linear with biphasic elimination: 175 mg/m² paclitaxel as 24h or 3h infusions have Cmax, T1/2, and clearances of 0.5 ± 1 or 5.9 ± 0.9 µmol/L, 14.8 ± 8.9 or 6.5 ± 3.4 h, and 13.9 ± 4.2 or 11.4 ± 1.8 L/h/m², respectively. These PK parameters may be further altered as a result of interactions with substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4. The drug is usually administered after premedication with dexamethasone and drugs to counteract histamine release (initially cimetidine and diphenhydramine) and diminish the occurrence of hypersensitivity reactions during the first few minutes of drug exposure on the first or second cycles (some of these reactions were fatal before awareness and these procedures for drug administration became standardized).

**Docetaxel** (Taxotere) is somewhat less lipophilic than paclitaxel, but still requires solubilizing with each 20 mg of Taxotere (Sanofi-Aventis) with 1040 mg of polysorbate (Tween) 80 and 13% ethanol per 1.5 mL. The area-under-the-curve (AUC) of docetaxel is dose-proportional in the usual clinical range (75-100 mg/m²) with a clearance of 21 L/h/m² in studies of one-hour infusions. It also undergoes oxidative metabolism by the CYP3A subfamily. Dexamethasone is also used routinely to counteract some hypersensitivity reactions that may occur and to minimize edema from ‘capillary leak’ syndrome that was recognized early in its development.

**Nab-paclitaxel** (nanoparticle albumin-bound paclitaxel, Abraxane) was approved in 2005 for the treatment of breast cancer at a dose of 260 mg/m² every 3 weeks given in a less than 30 minute infusion, usually without any pre-medication –constituting an advantage particularly when glucocorticoids are contraindicated (such as in the presence of viral hepatitis or hard-to-control diabetes mellitus). PK in comparison to paclitaxel include: 1) linear clearance that is roughly 50% greater than for an equivalent paclitaxel dose, 2) also it has up to 50% greater volume of distribution, and 3) intratumoral transport of nab-paclitaxel transcytosis mediated by SPARC (secreted protein, acidic rich in cysteine) leading to higher accumulation of drug.

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