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Albumin-Bound Paclitaxel In Metastatic Breast Cancer

A Viewpoint by Nuhad Ibrahim

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Conventional paclitaxel (CrEL-paclitaxel) is very effective in the treatment of breast cancer as a single agent or in combination therapy. Being water insoluble, Cremophor®-EL is used as the solvent to allow its intravenous administration. Such a solvent may increase the adverse effects of the formulation and result in reduced tolerability. Administration of higher doses of CrEL-paclitaxel is compromised by lack of increasing activity[1] paralleled by increasing adverse events. These solvent-enhanced adverse events include hypersensitivity, increased myelosuppression and neuropathy.

130-nanometre albumin-bound paclitaxel (*nab*™-paclitaxel) [ABRAXANE®] is a water-soluble formulation of paclitaxel. Albumin serves as a natural carrier of the hydrophobic molecule, in contradistinction to the large micelles formed by CrEL-paclitaxel. This formulation achieved the purpose of (i) eliminating hypersensitivity reactions and therefore the need for corticosteroid and histamine H2-receptor antagonist premedication; (ii) eliminating the need for special tubing; (iii) reducing the period of drug administration (30 minutes vs 3 hours); (iv) improving tolerance (decreasing the frequency and sensitivity of myelosuppression and neurotoxicity); and (iv) not compromising clinical efficacy, rather it resulted in its enhancement.

To achieve its effect, a cytotoxic drug needs to be transported from the blood vessel to the tumour vascular bed and thereafter intracellularly to exert its cytotoxic effect. It is traditionally held that drugs usually leak from the lumen of tumour microvasculature into the tumour interstitium via inter-endothelial junctions. Albumin-bound drugs may bind to a protein receptor (gp 60) on the luminal surface of the endothelium and activate caveolin-1, found on the interstitial surface of the endothelium, resulting in budding (caveolae formation) and internalisation of the drug, and its release in the tumour interstium. This process enhances drug delivery 3- to 4-fold, compared with intercapillary leakage of large CrEL-paclitaxel micelles.

Furthermore, transport of the drug from the tumour interstitium to the interior of tumour cells is also enhanced. Albumin-paclitaxel complexes bind to SPARC (Secreted Protein Acidic and Rich in Cysteine), which enhances the transport and intracellular accumulation of paclitaxel.

nab-Paclitaxel is therefore, an improved formulation of CrEL-paclitaxel by virtue of its increased tolerability and enhanced antitumour activity. It has received approval from the US FDA for the treatment of metastatic breast cancer. It also introduces a new technology for hydrophobic drug delivery. Greater understanding of the physiological role of albumin in drug delivery may allow for the selection of tumours for preferential treatment with *nab*-drugs based on the level of SPARC expression. ▲

Reference

1. Winer EP, Berry DA, Woolf S, et al. Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: cancer and leukemia group B trial 9342. J Clin Oncol 2004 Jun 1; 22 (11): 2061-8