S05-4 Clinical and experimental evidence suggesting the usefulness of pemirolast for prevention of hypersensitivity reactions to paclitaxel

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Paclitaxel (PTX) is a potent anticancer agent used for ovarian cancer, breast cancer, stomach cancer and endometrial cancer. However, its use is often limited by the incidence of myelosupression and peripheral neuropathy. Moreover, PTX causes severe hypersensitivity reactions (HSRs), thus, premedication for prophylaxis of HSRs is essential, although the mechanisms underlying PTX-induced HSRs remain to be clarified. We established an animal model of PTX-induced HSRs and the modes of action of PTX were elucidated. PTX (15 mg/kg, i.v.) caused pulmonary injury, as characterized by an increase in pulmonary vascular permeability and edema. The arterial PaO_2 decreased, while $PaCO_2$ increased, transiently after PTX injection. The PTX-induced pulmonary vascular hyperpermeability was blocked by dexamethasone but not by histamine H_1 or H_2 antagonists. Moreover, the pulmonary injury was reversed by sensory denervation with capsaicin or NK_1 and NK_2 antagonists. Indeed, the contents of such sensory peptides as substance P and neurokinin A were elevated in rat bronchoalveolar lavage fluid after PTX injection. Notably, pemirolast, a mast cell stabilizer, strongly suppressed PTX-induced pulmonary injury and elevation of sensory peptides. In patients with ovarian cancer, PTX increased plasma level of substance P but not histamine. A single oral treatment with pemirolast (10mg) prevented the incidence of HSRs associated with PTX. These findings suggest that PTX induces HSRs by facilitating the release of sensory peptides and that pemirolast is potentially useful for the prophylaxis of HSRs associated with PTX.