Section: *Prevention, Risk Reduction, and Hereditary Cancer: Prevention of Primary and Secondary Malignancies*

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Abstract Title:

Reduction in local tumor recurrence in a murine R2 resection model comparing locally administered docetaxel-releasing product, OncoPLEX, versus systemic docetaxel.

Background

Local recurrence (LR) negatively impacts long-term survival and patients' quality of life in many solid tumor malignancies, despite advances in surgical techniques and neoadjuvant and adjuvant treatments. Systemic treatment-related morbidity and mortality remains an unmet need, especially if only an R2 resection is achievable. OncoPLEX is a biodegradable, extended-release formulation of docetaxel that is applied in the form of a paste to the resection bed at surgery. We evaluated OncoPLEX efficacy in preventing local recurrence in an R2 tumor resection model generated with cell lines that exhibit high or low docetaxel sensitivity.

Methods

Cell lines sensitivity to free docetaxel and OncoPLEX-released docetaxel were determined in a cytotoxic assay. CT26 (murine colorectal carcinoma--resistant) and U-87 (human primary glioblastoma—sensitive) were tested. A murine subcutaneous (SC) tumor resection model using a predetermined tumor size (400-600 mm^3) and a standardized R2 resection (~90%) was developed. OncoPLEX was applied once on the tumor bed post-resection, docetaxel was IV injected every 4 days (6 times total), and animals were followed for tumor regrowth. The overall docetaxel dose in OncoPLEX (0.78 mg docetaxel) is lower than the maximal tolerated dose and non-lethal reported dose (TAXOTERE [10 mg/kg IV]; prescribing information).

Results

The IC_{50} concentrations of free docetaxel in CT26 and U-87 cell lines indicated resistance and sensitivity to docetaxel respectively (112.6 nM vs 4.2 nM). The cytotoxic potency of OncoPLEX-released docetaxel exhibited a similar relationship with greater potency (IC_{50} values in CT26 56.7 vs. 1.2 nM in U-87). At the completion of the CT26 SC study (37 days), there were more tumor-free animals in the OncoPLEX group (6/8, 75%) compared with the control IV docetaxel treated (3/8, 38%) or the untreated control (0/8, 0%). A similar trend was observed in the U-87 study; OncoPLEX (4/10, 40%), Control intraperitoneal-injected taxel (2/10, 20%), and untreated control (0/10, 0%). In both studies, the average tumor volume was significantly smaller with either OncoPLEX or systemic treatment compared with untreated controls (CT26: 375 mm^3, 485 mm^3 and 1500 mm^3 ($p<0.05$); U-87, 403 mm^3, 780 mm^3 and 2059 mm^3; $p<0.001$). There was no effect on behavior or weight in the OncoPLEX treated animals.

Conclusions

Locally administered OncoPLEX in this R2 resection model reduced local tumor recurrence and systemic adverse outcomes. OncoPLEX offers a potentially enhanced local adjuvant chemotherapy option with reduced side effects for solid tumors, independent of the tumor sensitivity or resistance to docetaxel.