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Oxaliplatin Induces the Expression of Genes Involved in Capecitabine Activation: Preliminary Results of a Phase I Pharmacodynamic Study in Esophageal Cancer

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Background: Capecitabine is activated to 5-fluorouracil (5-FU) in three enzymatic steps involving carboxylesterase (CE), cytidine deaminase (CDA), and thymidine phosphorylase (TP). Our in vitro studies indicate that oxaliplatin induces CE gene expression. 5-FU, oxaliplatin, and radiation (RT) is an effective neoadjuvant regimen for esophageal cancer.¹ This study explored whether oxaliplatin induces expression of genes related to capecitabine activation in tumor biopsies and peripheral blood mononuclear cells (PMN), and correlated these changes with oxaliplatin pharmacokinetics and treatment response in a phase I study of neoadjuvant oxaliplatin, capecitabine, and radiotherapy for patients with esophageal cancer.

Materials and Methods: Oxaliplatin (85 mg/m²) was administered on days 1, 15, and 29. Capecitabine at dose levels (DL) of 1,000 mg/m² (DL I), 1,250 mg/m² (DL II), or 1,500 mg/m² (DL III) was administered from Monday to Friday, weekly, with RT (1.8

Gy daily \times 28). Capecitabine and RT were started on day 3. Expression of CE, CDA and TP genes in tumor biopsies and PMN was evaluated before treatment and on day 2 (24 hours post-oxaliplatin) using quantitative real-time polymerase chain reaction (QRT-PCR) with comparative C_T method. After chemoradiation, patients underwent esophagectomy. Platinum in plasma ultrafiltrate was measured using atomic absorption spectrophotometry, and pharmacokinetic parameters were derived using WinNonlin. Statistical techniques included the signed rank test and the Spearman rank correlation.

Results: Sixteen (16) patients were treated (3 at DL I, 6 at DL II, and 7 at DL III); 12 patients underwent esophagectomy. Four patients had complete responses, 2 had microscopic residual disease (< 1 cm), 5 were downstaged, 3 patients progressed, and 4 patients did not have surgery (1 expired, 1 refused, and 2 failed surgical clearance). Tumor biopsy and PMN gene expression data were available for 15 patients. Induction of one or more of the three genes was noted in tumor biopsies from several patients. CE expression in the day-2 tumor biopsies and the fold increase in its expression from pretreatment level showed significant correlation to response ($P \leq .03$). TP expression in day-2 tumor biopsies was also related to response ($P = .03$). Induction of one or more genes by oxaliplatin may be associated with response, and lack of induction with progressive disease. The changes in gene expression did not correlate with the pharmacokinetics of oxaliplatin. CDA and TP had similar levels of expression in tumor biopsies and PMN; CE had lower expression in PMN ($P < .01$). No correlation was noted between gene expression in tumor biopsies and PMN.

Conclusions: The maximal tolerated dose was 85 mg/m² of oxaliplatin, 1,250 mg/m²/day of capecitabine, and 50.4 Gy of radiation. Oxaliplatin up-regulated expression of the carboxylesterase gene, and this up-regulation correlated with response. PMN do not serve as a surrogate tissue for studying expression changes for these genes.

Reference

1. Khushalani NI, Leichman CG, Proulx G, et al: Oxaliplatin in combination with protracted-infusion fluorouracil and radiation: report of a clinical trial for patients with esophageal cancer. *J Clin Oncol* 20: 2844-2850, 2002

Fig 1. Changes in carboxylesterase (CE) expression from baseline to 24 hours after oxaliplatin (OXP) in tumor specimens and peripheral blood mononuclear cells (PMN). Each patient's response is coded as follows: 0 = unevaluable, 1 = progressive disease, 2 = partial response, 3 = minimal residual disease, and 4 = pathologic complete response.

