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Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONcePT

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Background: Oxaliplatin is an integral component of colorectal cancer treatment, but its use is limited by neurotoxicity. The Combined Oxaliplatin Neurotoxicity Prevention Trial (CONcePT) tested intermittent oxaliplatin (IO) administration and the use of concurrent calcium and magnesium salts (Ca/Mg), two modifications intended to reduce neurotoxicity and extend the duration of treatment.

Patients and methods: In this trial involving double randomization, 140 patients were randomized to receive modified FOLFOX7 plus bevacizumab with IO (eight-cycle blocks of oxaliplatin treatment) versus continuous oxaliplatin (CO); and Ca/Mg versus placebo (pre- and postoxaliplatin infusion). The primary end point was time-to-treatment failure (TTF).

Results: One hundred thirty-nine patients were entered and treated up to the point of early study termination due to concerns by the data-monitoring committee (DMC) that Ca/Mg adversely affected tumor response. Tumor response was not a study end point. Given DMC concerns, an additional independent, blinded radiology review of all images showed no adverse effect of treatment schedule or Ca/Mg on response by Response Evaluation Criteria In Solid Tumors. The IO schedule was superior to CO [hazard ratio (HR) = 0.581, $P = 0.0026$] for both TTF and time-to-tumor progression (TTP) (HR = 0.533, $P = 0.047$).

Conclusions: An IO dosing schedule had a significant benefit on both TTF and TTP versus CO dosing in this trial despite the very attenuated sample. There was no effect of Ca/Mg on response.

Key words: bevacizumab, calcium and magnesium salts, colorectal cancer, FOLFOX, intermittent, drug-induced neurotoxicity

introduction

Oxaliplatin with infusional 5-fluorouracil (5-FU) and leucovorin (LV) (FOLFOX) is an established treatment of metastatic colorectal cancer (CRC) [1–5]. Oxaliplatin-based therapy also shows improved efficacy combined with bevacizumab (BEV) [6–8]; however, neurotoxicity is a dose-limiting adverse event (AE) for oxaliplatin [3, 4, 9, 10] and the maximal benefit of BEV cannot be achieved without treatment to disease progression [7]. This necessitates a strategy to 'optimize' use of oxaliplatin. Intermittent oxaliplatin (IO) administration and prophylactic calcium/magnesium salts (Ca/Mg) are two treatment modifications that may reduce neurotoxicity, allowing more extended use of oxaliplatin [11, 12].

We report the findings of Combined Oxaliplatin Neurotoxicity Prevention Trial (CONcePT). The objective was to compare efficacy and safety (including neurotoxicity) of IO ± Ca/Mg versus continuous oxaliplatin (CO) ± Ca/Mg as first-line treatment in patients with advanced CRC receiving modified FOLFOX7 (mFOLFOX) plus BEV. Patients were originally randomized to receive either Ca/Mg or placebo combined with the IO or CO regimen; however, a protocol amendment after 140 patients enrolled allowed Ca/Mg prophylaxis in all patients [13, 14]. An unplanned interim analysis by the data-monitoring committee (DMC) indicated a possible negative effect of Ca/Mg on tumor response (which was not a study end point); the study was terminated, with treatment and follow-up of all patients immediately stopped per DMC mandate. Herein, efficacy and safety data are presented for patients randomized to the original 2 × 2 factorial design.

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