Optimized Dosing Improves Outcomes in Colorectal Cancer

5-Fluorouracil (5-FU) is the backbone of colorectal cancer chemotherapy regimens. Traditionally, standard dosing recommendations for 5-FU have relied on calculating a patient's body surface area (BSA). However, with BSA based dosing, there is wide inter- and intra-individual variability in the systemic concentration of chemotherapy agents, including 5-FU. Additionally, evidence supports a close association between 5-FU exposure, efficacy, and toxicity, rather than the dose administered. Previous studies have shown that patients with 5-FU exposure (expressed as Area Under the Curve or AUC) of <20 mg•h•L⁻¹ were underdosed and had decreased responses, while patients with 5-FU AUC of >24 mg•h•L⁻¹ were at higher risk of severe adverse toxic effects.* The authors of this paper report on a phase III, multi-center, randomized study comparing conventional BSA dosing of 5-FU plus folinic acid (leucovorin) to pharmacokinetically-guided dose adjustment of 5-FU.


PURPOSE: To compare patients dosed with infusional 5-FU based upon body-surface area with patients receiving pharmacokinetically-guided dose adjusted 5-FU. Survival, tumor response, treatment efficacy, and toxicity were examined.

DESIGN: 208 metastatic colorectal cancer patients from five hospitals were randomized to two study arms. In Arm A, patients were given a constant 1,500 mg/m²/wk dose of infusional 5-FU over 8 hours, except if toxicity necessitated a reduction in dosage. In Arm B, patients were initially given a 1,500 mg/m² dose of 5-FU over 8 hours, which was adjusted weekly based upon calculated AUC from the previous cycle until the AUC reached the therapeutic range. Dose adjustment was based upon a previously defined protocol (see below). Therapeutic range was defined as AUC of 20-24 mg•h•L⁻¹.

RESULTS: The majority of patients in Arm B required a dose-adjustment of 5-FU. 94% of patients achieved the target range in a mean of 4 cycles. In Arm B, the mean dosage of 5-FU after 3 months of treatment was 1,790 mg/m²/week with a range of 765 to 3300 mg/m². In Arm B, objective response rate and median overall survival were higher, as compared to Arm A, without dose adjustment. Toxic adverse effects were significantly less frequent (eg, diarrhea reduced by 78%) and less severe in the pharmacokinetic-dose adjusted Arm B when compared with Arm A (P=.003).

Response Rate and Survival for Optimized Dose Adjustment Versus Body Surface Area Based Dosing

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<tr>
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<th>Optimized Dose Adjustment</th>
<th>Body Surface Area Based Dosing</th>
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<tbody>
<tr>
<td>Objective Response Rate (P=.004)</td>
<td>33.7%</td>
<td>17.3%</td>
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<tr>
<td>Median Overall Survival (P=.08)</td>
<td>22 months</td>
<td>16 months</td>
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5-FU: Dose Adjustment Protocol

* Area Under the Curve (AUC) represents the concentration of 5-FU in the circulatory system over a given time.