Tegafur and 5-Fluorouracil pelvic tissues concentrations in rectal cancer patients treated with preoperative chemoradiation. The processed sample stability investigation and their impact in the reability of the data

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Objectives

The aim of this study was to quantify tegafur and 5-Fu concentrations in tissues of rectal cancer patients treated with preoperative chemoradiation and to correlate drug concentrations with cancer downstaging effects. Also was conducted a limited stability study.

Patients and methods

Three tissue samples of 16 patients with locally advanced rectal cancer treated with preoperative pelvic irradiation sensitized with oral tegafur during the course of radiotherapy in 5 to 6 weeks before surgery (5 to 6 weeks after the completion of chemoradiation) were analyzed. Seven patients received a precharge dose of tegafur 24 hours before surgery.

Tegafur and 5-Fu concentrations, were determined according to a high performance liquid chromatography (HPLC) method developed and validated by the pharmacokinetic laboratory of the Pharmacy Department at the University Hospital of Navarra.

Patients, tumor and treatment characteristics, 5-Fu and tegafur concentrations and tumor response were recorded in a database. The correlation of 5-Fu concentrations in pelvic tissues and tumor downstaging effects was performed exclusively in patients receiving precharge dose of tegafur. The small cohort of patients analyzed in the present study limits the statistical study. Stability study of processed samples was investigated as a requirement of the analytical method validation, by reinjecting the samples (hold at room temperature in the auto-injector) at different time intervals during 17 days.

Results

Table 1. Tegafur and 5-Fluorouracil tissue concentrations

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tegafur concentrations (ng/g)</th>
<th>5-Fu concentrations (ng/g)</th>
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</thead>
<tbody>
<tr>
<td>Peri-rectal fat</td>
<td>1333 (314 - 3135.3)</td>
<td>72 (12.1 - 205)</td>
</tr>
<tr>
<td>Normal mucosa</td>
<td>4905.8 (1563-7847)</td>
<td>179 (2.2 - 64.4)</td>
</tr>
<tr>
<td>Residual tumor</td>
<td>3847 (1563-7847)</td>
<td>252 (3.8 - 60)</td>
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* Tegafur 1200 mg oral 24 hours before surgery. Concentrations are expressed as mean (range)

In eight of the nine patients without precharge dose was possible to obtain detectable levels of tegafur but only in one patient 5-Fu levels were detectables. In tegafur pre-charged patients both tegafur and 5-Fu were present in all tissue samples with exception of 2 fat samples.

Fig 1: Correlation between 5-FU concentration in residual tumor tissue and downstaging effects

Both tegafur and 5-Fu levels were higher in tumor samples than other sites and show a clear tendency toward a correlation between level of 5-Fu present in the residual tumor and cancer downstaging.

Stability study showed a progressive increase of 5-Fu levels with time with no change in tegafur values; so we hypothesize about the presence of a chemically labile metabolic intermediates that spontaneously cleave to 5-Fu.

Conclusions

- A prospective study with a larger cohort of patients is necessary to confirm these results and to evaluate if tumor uptake of fluoropyrimidine could be a prognostic indicator of downstaging.
- Research should also be required to characterize the metabolic intermediates found in the stability study.