Evaluation of lipid profiles in patients treated with capecitabine

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1. Introduction

Antineoplastic drugs have many side effects and have impact on quality of life. Severity and frequency of the side effects vary depending on each person and the type of drugs. It is necessary to track and thus prevent possible side effects (1–4). Capecitabine is a prodrug of 5-fluorouracil and has shown significant antitumor activity. The main adverse effects are hand-foot syndrome, diarrhea, and dermatitis. In recent years, hypertriglyceridemia has been reported in patients treated with capecitabine. Dyslipidemia is a rare but important side effect of capecitabine. The aim of this study is to examine the changes in lipid levels during capecitabine treatment and to raise awareness of pharmacovigilance.

Materials and methods: In this retrospective study, it was aimed to analyze lipid metabolism after capecitabine treatment and is intended to contribute to the formation of a pharmacoepidemiological database. For this purpose, triglyceride, cholesterol, HDL, LDL, ALT, AST, ALP, MCV, and Hb blood levels of 57 patients treated with capecitabine at the Department of Medical Oncology, Faculty of Medicine, Çukurova University, were examined before and after five cycles of treatment.

Results: Blood triglyceride and cholesterol levels were significantly increased after capecitabine treatment. The increase in triglyceride levels was higher than the increase in cholesterol levels.

Conclusion: In the light of these findings, monitoring of the lipid profile should be considered in cancer patients treated with capecitabine.

Key words: Capecitabine, triglycerides, cholesterol

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The results are interpreted as average ± standard deviation, median (min–max), n, and as percentage. A P value less than 0.05 (P < 0.05) was accepted as statistically meaningful.

3. Results
A total of 57 patients were treated with capecitabine in cases of breast, colon, gastric, lung, pancreas, rectum, and renal cell cancer. Thirteen patients had DM, while 21 patients had dyslipidemia before capecitabine treatment (Table 1).

After 5 cycles of capecitabine treatment, triglyceride median level of patients increased from 170 (69–657) mg/dL to 321 (228–871) mg/dL and cholesterol average level increased from 187.7 ± 50 mg/dL to 242.3 ± 52.7 mg/dL and these increases were statistically significant (P < 0.01).

While in patients with no history of dyslipidemia the median triglyceride level was 137 (69–197) mg/dL before treatment, this level increased to 292 (228–542) mg/dL. On the other hand, for the patients with dyslipidemia, triglyceride median level was 223 (135–560) mg/dL before treatment and this level increased to 466 (251–871) mg/dL after treatment (Figure 1).

Cholesterol average level of patients without a history of dyslipidemia was 164.4 ± 36.1 mg/dL before treatment and this level increased to 238.7 ± 62.1 mg/dL after treatment. Cholesterol average level of patients with a history of dyslipidemia was 227.7 ± 45.4 mg/dL before treatment and this level increased to 248.8 ± 34.8 mg/dL after treatment (Figure 2).

Triglyceride median levels in patients with no history of DM were 161.5 (69–657) mg/dL and 292 (228–620) mg/dL before and after capecitabine treatment, respectively. Triglyceride median levels in patients with a history of DM were 187.5 (125–436) and 668.5 (331–871) mg/dL before and after capecitabine treatment, respectively (Figure 3).

Cholesterol average levels in patients without a history of DM were 183.3 ± 40.3 mg/dL and 235.7 ± 50.5 mg/dL before and after capecitabine treatment, respectively. Cholesterol average levels of diabetic patients were 210.1 ± 50.2 mg/dL and 257.3 ± 35.8 mg/dL before and after capecitabine treatment, respectively (Figure 4).

HDL, LDL, AST, ALT, ALP, and Hb levels before and after treatment did not show significant change (P > 0.05). MCV levels were higher after treatment compared to pretreatment levels (P < 0.05) (Table 2).

4. Discussion
Changes in lipid profile in cases treated with capecitabine were examined in 57 patients. Cholesterol and triglyceride levels were increased in patients treated with capecitabine but changes in HDL and LDL levels were not significant after capecitabine treatment. Moreover, there were no changes in the levels of ALT, AST, or ALP.

Table 1. Characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Patients</td>
<td>57</td>
</tr>
<tr>
<td>Mean age</td>
<td>56.1 ± 11.5</td>
</tr>
<tr>
<td>Female/male</td>
<td>46/11</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>37 (61.4)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (22.8)</td>
</tr>
<tr>
<td>DM</td>
<td>13</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>21</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>20 (35)</td>
</tr>
<tr>
<td>Combination with capecitabine</td>
<td>37 (65)</td>
</tr>
</tbody>
</table>
Although National Cancer Institute Common Toxicity Criteria grade 3 or 4, hypertriglyceridemia is listed in the manufacturer's product literature and has been reported as an uncommon (0.1%–1%) toxicity (5–15). Data about the effect of capecitabine on lipid profile for clinical practice are limited. For example, strong decreases in HDL levels after capecitabine (from 46 to 4.8 and 114 to 32) in 2 cases have been reported by Duman et al. (5). In a prospective study, hypertriglyceridemia has been reported in 3.7% of 304 cases and this is important information for clinicians to be aware of the risks of abnormal lipid profile in patients treated with capecitabine (6). The incidence of hypertriglyceridemia was found to be higher than that of hypercholesterolemia by Bar-Sela et al. and 4 severe and 19 mild cases of hypertriglyceridemia and hypercholesterolemia were reported in their study covering 102 cases (7).

It is very well known that hypertriglyceridemia and hypercholesterolemia may be related to diet, weight gain, obesity, alcohol consumption, diabetes mellitus, and nephrosis (5,7–13). However, the declining trend in lipid levels after capecitabine cessation supports the correlation between capecitabine and dyslipidemia. In our study group 13 patients had a history of diabetes mellitus and 21 patients had dyslipidemia. Increases in levels of triglyceride and cholesterol were greater in these patients. This situation suggests that clinicians must be more careful about lipid profile in patients with diabetes mellitus and/or dyslipidemia when planning capecitabine treatment and antilipemic treatment if necessary. Since capecitabine is given for longer in many cases, this will be vital for morbidity in the cases. It is very important in patients with cancer and comorbid conditions.

Although the etiology of capecitabine-induced hypertriglyceridemia and hypercholesterolemia is unknown, there are 3 hypotheses about this association (5–7,10–16). The first of these mechanisms is related to thymidine phosphorylase. It is well known that capecitabine is converted by thymidine phosphorylase to 5-FU. Because a previous study investigating the effect of 5-FU on serum lipid levels showed a significant reduction in total cholesterol in both patients and animals, hypertriglyceridemia may be attributed either to capecitabine itself or to precursor of 5-FU (5–7,11–16). The second is related to a lipoprotein lipase (LPL) defect. A defect of LPL is linked with an accumulation of chylomicrons and/or of very low-density lipoprotein (VLDL) (6,7,10,12–16). Kurt et al. suggest that CIHT may appear more readily in individuals with hereditary LPL deficiency (14). It is worth noting that LPL defect also occurs in the case of an increase in its inhibitor (apolipoprotein CIII) and/or a decrease in its activator (apolipoprotein CII). However, the link between capecitabine and apolipoprotein CII/CIII levels has never been explored (6,7,10,12–16). The third is capecitabine causes pancreatic inflammation and this inflammation causes hyperglycemia and hypertriglyceridemia (5,10,12,13). Triglyceride levels have been found to be increased from 270 to 9063 mg/dL and glucose levels have been found to be increased from 90 to 350 mg/dL in 2 cases reported by Duman et

Table 2. MCV levels of the patients for before and after (1–5) the capecitabine treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td>MCV* fL</td>
<td>85.7 ± 8.3</td>
<td>88.8 ± 9.6*</td>
<td>91.4 ± 11.5*</td>
<td>90.1 ± 12.6*</td>
<td>86.5 ± 9.8</td>
<td>86.8 ± 9.5</td>
</tr>
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Average ± SD (*P < 0.05)
al (5). Similar increases have been reported by Han and Huang (13). In the present study, in order to understand the relations of triglyceride and cholesterol levels with liver enzymes levels of ALT, AST, and ALP were observed and no statistically meaningful relations were found.

A significant increase in MCV was found in our patients after capecitabine treatment. We did not find folate or vitamin B₁₂ deficiency in our patients. This has been attributed to capecitabine-induced macrocytosis as suggested by Jung and Wenzel (17,18).

In conclusion, capecitabine causes disturbances in the serum lipid profile especially in patients with underlying dyslipidemia and/or diabetes mellitus. Since hypertriglyceridemia has serious acute and chronic metabolic complications (such as acute pancreatitis), serum lipid levels must be closely monitored in patients with diabetes and dyslipidemia under capecitabine treatment. Increase in MCV during capecitabine treatment is an interesting finding and the pathogenesis is not clear.

References